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Preface

Volume 67 of *Advances in Heterocyclic Chemistry* commences with an overview of aromatic biheterocycles written by P. J. Steel (University of Canterbury, New Zealand), which covers biheterocycles containing two identical N-, O-, or S-containing aromatic heterocyclic rings linked by a single bond between these two rings. No previous review has been available on this group of compounds, which is finding increasing importance as chelating ligands and in various aspects of materials chemistry.

The second chapter in this volume, by Stanislav Radl (Prague, Czech Republic), covers 1,2,4-triazoline-3,5-diones, which comprise the most important group of cyclic aza-dicarbonyl derivatives. These compounds, of particular importance as components in cycloadditions, have not been reviewed recently.

Ping Lue and John Greenhill (of Albright and Wilson Americas, Virginia, and of the University of Florida, respectively) contribute a survey of the applications of enaminones in heterocyclic synthesis. This chapter updates a review written 20 years ago on the chemistry of enaminones by John Greenhill and is particularly timely as the majority of the new work has been in heterocyclic synthesis.

The fourth chapter in the present volume is an account of the synthesis of quaternary benzo[*c*]phenanthridine alkaloids and has been written by Simon Mackay, Otto Meth-Cohn, and Roger Waigh, all of the University of Sunderland, U.K.

The final chapter of Volume 67 has been authored by El Sayed El Ashry (University of Alexandria, Egypt). Professor El Ashry's subject is the acyclonucleosides. Indeed, this chapter is the first of a trilogy of chapters that will appear in Volumes 67, 68, and 69. The whole subject of acyclonucleosides has been organized so that the present chapter deals with *seco*-nucleosides (i.e., with a single-bond disconnection). Part 2, which is planned to appear in Vol. 68, will cover *diseco*-nucleosides, and Part 3 (Vol. 69) will cover *triseco-*, *tetraseco-*, and *pentaseco*-nucleosides. These compounds are of considerable interest because of the antiviral activity of many of them.

ALAN R. KATRITZKY

ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 67

Aromatic Biheterocycles: Syntheses, Structures, and Properties

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I. Introduction

Aromatic biheterocycles, as defined in this review, contain two identical nitrogen-, oxygen-, and/or sulfur-containing aromatic heterocycles (including their benzo derivatives), which are linked by a single bond between the two heterocyclic rings. Although such compounds have been known and studied for well over a century, there has been a marked recent increase in interest in this area. For example, current research on bipyrroles and bithiophenes reflects their relevance to the important conducting polymers polypyrrole and polythiophene. Many naturally occurring compounds contain aromatic biheterocycles as structural subunits; a selection is shown in Fig. 1. The isolation, structure determination, and total syntheses of such natural products have been much studied in recent years.

One of the most common uses of biheterocycles is as chelating ligands in coordination, organometallic, and analytical chemistry. Although 2,2′-bipyridine has been used for this purpose for over a century, it has only recently become recognized that other biheterocycles have very different molecular orbital energy levels and, hence, very different interactions with the *d* orbitals of coordinated transition metals. As a result, new studies have shown that it is possible to tune the physicochemical properties of such metal complexes by judicious choice of biheterocyclic ligands. Furthermore, biheterocyclic ligands with multiple heteroatoms in the rings can act as binucleating ligands that bridge two metal centers. Such compounds may exhibit various types of metal–metal interactions, such as electron transfer, energy transfer, and magnetic interactions, and have been the focus of

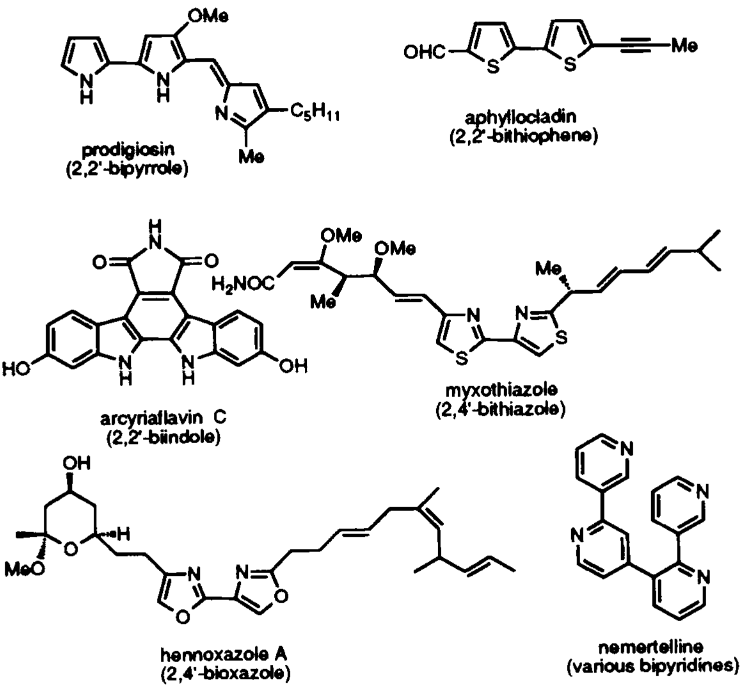


FIG. 1. Selected natural products containing biheterocyclic subunits.

much recent work. Chelating biheterocycles have also been employed as subunits in molecular hosts, such as macrocycles and cryptands, and as components in the construction of many larger supramolecular species, such as helicates, catenates, rotaxanes, and dendrimers.

Several new alternatives to the classical methods of synthesis of biheterocycles have been developed. Most notable among these are low-valent transition metal-catalyzed homo-coupling reactions, which are particularly applicable to the synthesis of biheterocycles, and which give much better yields than the earlier Ullmann and Busch procedures. Furthermore, unsymmetrical biheterocycles are now more readily available by way of palladium-catalyzed cross-coupling reactions, such as the Stille and the Suzuki procedures. Thus, many new members of the biheterocyclic series are now available for study. As a consequence of the increased sophistication of molecular structure determination techniques, aromatic biheterocycles have been the subject of many recent spectroscopic and X-ray crystallographic studies, as well as numerous molecular orbital and molecular mechanics calculations.

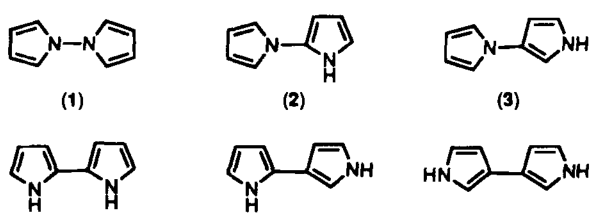
The chemistry of aromatic biheterocycles has not previously been reviewed; in view of the intense current activity in this area, a survey of the syntheses, structures, and chemistry of such compounds seems timely. The present report reviews these aspects of aromatic biheterocycles and their benzo derivatives. It is restricted in scope of five- and six-membered aromatic heterocycles in which the two identical heterocyclic ring systems are linked by a single bond. This excludes several groups of important compounds, such as molecules containing two different heterocycles, nonaromatic partially saturated biheterocycles, molecules linked through benzo rings, and molecules containing two heterocycles linked by a carbon, or heteroatom, bridge.

For each class of compounds, the different possible isomers are considered, their syntheses discussed, structural and spectroscopic studies surveyed, and their chemical reactions and applications reviewed. For the most part, emphasis is placed on the parent, unsubstituted compounds. It is hoped that this survey will prove useful to those working with biheterocycles, and serve to highlight the surprising number of compounds that have not yet been studied. The review provides complete coverage of the open literature up to the end of 1994, with selected 1995 references also included.

II. Five-Membered Rings: One Heteroatom

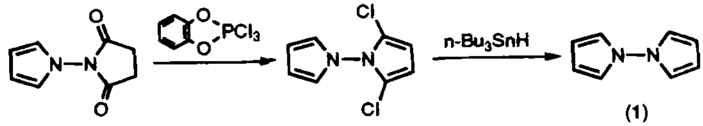
A. Bipyrroles

a. *Synthesis.* Four of the six isomeric bipyrroles (**1–6**) are known. Although several methods exist for the syntheses of substituted 1,1′-bipyrroles, these are not applicable to the preparation of the parent compound (**1**).



(1) (2) (3) (4) (5) (6)

The only reported preparation of **1** is that shown in Scheme 1, by means of reduction of a dichloro derivative (77S414). Substituted derivatives of **1** can be prepared by reactions of 1,4-diketones with hydrazine (04CB2183,



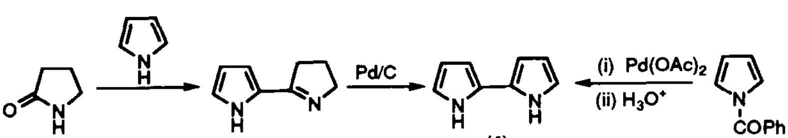
(1)

SCHEME 1

04CB2697); by reactions of *N*-aminopyrroles with 1,4-dicarbonyl compounds, or their equivalents (31JA2353; 69CB3268; 75T1549; 87LA893); by oxidations of pyrroles, or their metal salts (26G455; 51G276; 65B3124; 82CB2540); by reactions of *N*-pyrrolylsuccinimides with Wittig reagents (73CB1731; 77CB2765); and by rearrangements of three-membered ring precursors (70ZOR631; 93CB543). The unsymmetrical 1,2′- and 1,3′-bipyrroles, **2** and **3**, are not known. 3-Substituted derivatives of **3** have recently been prepared as analogues of the antifungal agent bifonazole (94FA229).

In contrast, 2,2′-bipyrrole (**4**) has been synthesized by various methods. It was first prepared by catalytic dehydrogenation of 2-(2′-pyrrolidinyl) pyrrole (62JA635), and shortly thereafter by the dehydrogenation of the corresponding, and more readily available, pyrroline (Scheme 2) (62JA2178). However, the yields of these dehydrogenations are rather low (64CJC1073). This problem can be circumvented by the condensation of Δ^3-pyrrolin-2-one with pyrrole, which leads directly to **4**, but the starting pyrrolinone is not readily available. The most efficient synthesis of **4** is that developed by Itahara (Scheme 2), involving the oxidation of 1-aroylpyrroles by palladium acetate, and subsequent mild hydrolysis of the resultant 1,1′-diaroyl-2,2′-bipyrrole [80JCS(CC)49]; this procedure has recently been modified [93JEC(355)115]. 2,2′-Bipyrrole has also been synthesized by two more circuitous routes [76CJC1083; 87ACS(B)426].

Substituted derivatives of **4** have been prepared by extensions of the procedures just described [64JOC2727; 65JOC3824; 80HCA1190; 86JCS(P1)455; 88JOC1405] and by other methods, including Ullmann coupling reactions (53JOC1413; 63JCS359; 67CB1704; 94JMC2797); transition-metal-catalyzed couplings of 2-lithiopyrroles (81CB3674; 94AGE736); and various cyclization procedures involving pyrrole ring formations (53JOC1406; 86T3753; 89JA776; 91KGS460; 95S276). Much of the work in this area



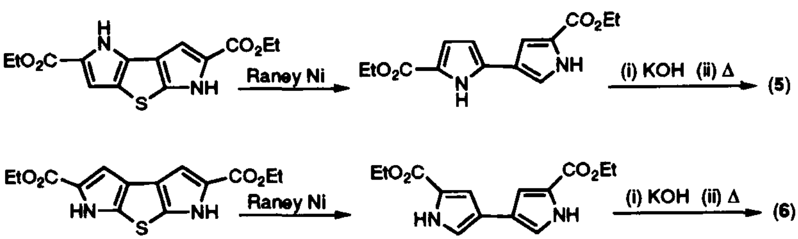
(4)

SCHEME 2

has been related to syntheses of the naturally occurring antimicrobial agent prodigiosin (Fig. 1), which contains **4** as a subunit (63JCS2326; 88JOC1405; 89TL1725). 2,2′-Bipyrrole also occurs as a subunit in many other naturally occurring systems, most notably the corroles, and, in a reduced form, in the corrins (e.g., vitamin B_{12}), and in many synthetic analogues of natural products, such as the sapphyrins (92T9661), porphycenes (87AGE928; 94AGE736, 94JMC2797; 95S1480) and other porphyrin isomers (94NJC1205), and hexapyrrins [94JCS(CC)1289]. The hexabromo derivative of **4** is produced by a marine organism (74MI1).

The 2,3′- and 3,3′-bipyrroles, **5** and **6**, are less readily available. This is partly because the logical precursors, the 2- and 3-halopyrroles, are very unstable compounds (76CJC1083; 90JOC6317). In fact, **5** and **6** have only been prepared by a complex sequence involving Raney nickel-induced desulfurization of thienodipyrrole diesters, as shown in Scheme 3 (76CJC1083). Substituted derivatives of both **5** and **6** have been known for some time (51G288; 52JPJ693; 70JOC2815). The *N,N*′-di(triisopropylsilyl) derivative of **6** has been prepared by homo-coupling of the corresponding 3-lithiopyrrole (90JOC6317). Other functionalized derivatives have been synthesized by a general procedure that was developed in the course of the synthesis of isochrysohermidin and involves a double reductive ring contraction of 4,4′-bipyridazines, formed from double Diels–Alder reactions of tetrazines (93JA11418).

b. *Physical Studies.* There have been no reported crystal structures of any of the unsubstituted bipyrroles, but most isomers have been the subject of many theoretical studies. In 2,2′-bipyrrole (**1**), the form in which the two rings are orthogonal has been calculated to be more stable than the coplanar form [83JST(104)197; 86CPL(130)285; 88JCC369]; this conclusion is supported by experimental observations [78T2301; 90JCS(F)3243; 91JCS(P1)1111]. Substituents in the 2 and 5 positions further destabilize



SCHEME 3

the coplanar form, and X-ray crystal structure determinations of 2,2′,5,5′-tetrasubstituted derivatives showed the rings to be orthogonal in the solid state [82CB2540; 91AX(C)1662]. Conversely, coplanarity between the rings can be encouraged by bridging between the 2- and 2′- (and 5- and 5′-) positions; an X-ray crystal structure of the diethano-bridged derivative showed the rings to be exactly coplanar [91AX(C)1662].

The 2,2′-isomer (**4**) has been the subject of much study, principally because of its relevance to the important conducting polymer, polyprrole, the formation of which involves **4** as an intermediate [93JEC(355)115, 93JEC(357)273]. There have been numerous theoretical studies of the conformation and electronic properties of **4** [82JCP(77)5030; 83JST(104)197; 84JCP(80)5643; 85JCP(83)1323; 86TCA(69)41; 88JCC369, 88M505; 92JCP(96)4464; 94CPL(221)507, 94CPL(224)213; 95JST(330)223]; the most reliable of these seem to suggest that the most stable conformation has a transoid configuration with a small twist about the inter-ring bond. Experimental studies of **4** include ultraviolet, infrared, and NMR spectroscopy (64JCS3315; 75CJC148), Raman spectroscopy (88SM(24)329], fluorescence spectroscopy (91JCP(95)4783], and electrochemical and spectroelectrochemical studies [93JEC(355)115].

Structural and physical studies of the two other C–C linked bipyrroles **5** and **6,** have been restricted to theoretical calculations; these suggest that the *s*-trans planar conformations are the most stable [83JST(104)197; 85JST(124)307; 88JCC369].

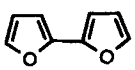
c. *Reactions.* The reaction chemistry of **1** is relatively unexplored. Formylation occurs to give the 2,2′-diformyl derivative as the major product (77S414) and this in turn has been used to synthesize annulene derivatives (81CB620). Attempts to effect a domino Diels–Alder reaction on the octamethyl derivative of **1** were not successful (89CB767).

The reaction chemistry of **4** is better studied. It has long been known to react with pyrrolyl aldehydes to give prodigiosin-type compounds (63JCS2326; 66JHC521) and reacts with triethyl orthoformate to give 1,9-bis(2-pyrrolyl)pyrromethene (93LA894). The dianion of **4** is alkylated by dichloromethane to produce a dimeric cyclophane (80HCA1190). Formylation of **4** occurs in the 5 (and 5′) position(s) (83JA6429). In order to avoid problems associated with the oxygen-sensitive nature of **4,** it has been protected as the *N,N*′-di-BOC derivative; this reacts with *N*-bromosuccinimide to give the 5,5′-dibromo derivative, which in turn is used to make polypyrroles (95MM116). A palladium complex of **4** is proposed to have an unusual bonding mode for the ligand (91MI1).

The reaction chemistry of **5** and **6** remains unexplored.

B. Bifurans

a. *Synthesis.* All three bifurans (**7–9**) are known. The 2,2′-isomer (**7**) is the best studied and has been synthesized by a variety of methods. It was first prepared by decarboxylation of the 3-carboxy derivative, prepared



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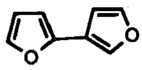

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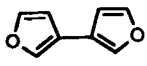
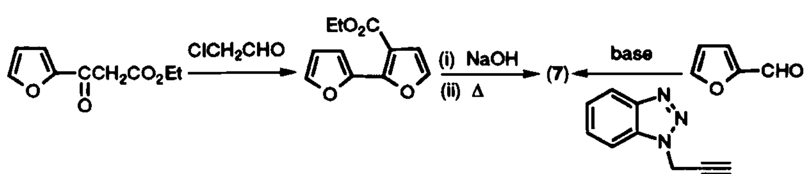


(9)

as shown in Scheme 4 (27JPJ501; 32HCA1066). It is more conveniently prepared from furan itself, either by direct coupling with palladium acetate (76MI1) or via the intermediacy of the 2-lithio- (81CB3667; 89MI3) or 2-chloromercury derivatives (76JOC2661; 77JOC1680). 2-Halofurans can also be coupled to **7**, either by direct nickel-mediated homo-coupling (94T11893) or via the derived Grignard reagent [67JCS(C)2011]. Palladium-catalyzed reaction of 2-furanoyl chloride with silanes produces **7** in high yield (90JOC5430). 2,2′-Bifuran (**7**) has also been prepared by methods involving furan ring formation via isoxazolines [87ACS(B)426] or, most recently, from furfural using benzotriazole chemistry (Scheme 4) (93JOC3038). 2,2′-Bifuran (**7**) has been identified in several natural sources of plant origin, most notably as an aroma constituent of coffee (67HCA628), and is formed in various Maillard reactions, such as that between xylose and lysine (93MI1).

Many substituted derivatives of **7** have been prepared by extensions of the procedures just discussed [71ZOR1062; 76JOC2075; 84S255; 86JCS-(CC)1255], as well as by other self-coupling reactions, such as Ullmann couplings [31RTC981; 66JCS(C)976] and photodimerizations [88ZOR459; 93G129; 94JCS(P1)1245]. Unsymmetrically substituted derivatives have been prepared by a diverse range of synthetic procedures involving furan ring formations [66JCS(C)976; 67KGS585; 78CB639, 78H(10)105; 83JHC-233; 85JOC4872; 88OM2346, 88TL3403; 89JOC4481; 91SL869, 91TL2913;



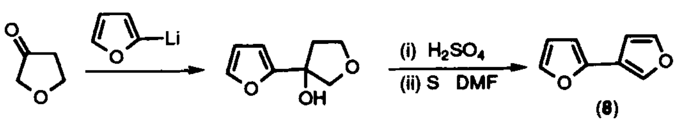
Scheme 4

93JCS(P2)1081, 93SL905]. 2,2′-Bifuran subunits have also been incorporated into annulenes (88AGE411), sapphyrins (92T9661), and crown ether-type macrocycles (82JOC3038).

There has been only one report of the synthesis of 2,3′-bifuran (**8**), which was obtained as an unstable oil by the method shown in Scheme 5 (71JOC1011). A few substituted derivatives have been prepared by ring-forming procedures [70JCS(C)476; 89T7631; 93JCR(S)68]. The 3,3′-isomer (**9**) was first prepared by an analogous method to that shown in Scheme 5 for the preparation of **8** (67RTC381). However, **9** is more conveniently prepared from commercially available 3-bromofuran with low-valent nickel reagents (84BCJ1887; 94T11893) or by lithium–halogen exchange and oxidative coupling (81CB3667). Again, substituted derivatives have been prepared by cyclization methods (35JA1947; 63TL1801; 74BSF2105), and in a recent study various symmetrical and unsymmetrical derivatives were prepared by self- and cross-couplings, respectively, of furanylboroxines (94JOC33).

b. *Physical Studies.* There have been no reported X-ray crystal structures of a parent bifuran, although structures have been reported of a trisubstituted derivative of **7** [90AX(C)1129] and of an annulene containing **7** as a subunit (88AGE411). There have been many theoretical studies of the conformations of all three bifurans, **7–9,** which generally agree that the two rings are coplanar (or nearly so in **9**) with small energy differences between the *s*-cis and *s*-trans forms, depending on the specific isomer and method of calculation [72T4419; 81IJQ383; 83JST(104)197; 84JST(108)199; 87JPC545; 88JCC369]. The spectroscopic and physical properties of **7** have been much studied [66JCS(C)976; 74SA(A)1413; 75JCS(CC)397; 77JCS(P2)314; 90PS(48)239; 92JCS(F)1863, 92MI1; 94MI1] and related to the structure and properties of polyfuran (91JPC9746). Similar studies of **8** and **9** have been restricted to ultraviolet spectra (71JOC1011) and photoelectron spectra (92MI1; 94MI1).

c. *Reactions.* Study of the reaction chemistry of these compounds has been restricted to 2,2′-bifuran (**7**), which displays typical furan-type reaction chemistry. For example, it is readily metallated (89SC787) and brominated

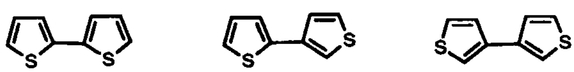


SCHEME 5

(90BCJ2828) in the 5- (and 5′-) position(s); undergoes a double Diels–Alder reaction with the reactive dienophile dimethyl acetylenedicarboxylate [67JCS(C)2327]; undergoes Vilsmeier formylation [67JCS(C)2011]; is readily hydrogenated (35JPJ741); and undergoes a ring-opening reaction with ethyl diazoacetate and dirhodium tetraacetate to give a diacylbutadiene (87HCA1429).

C. Bithiophenes

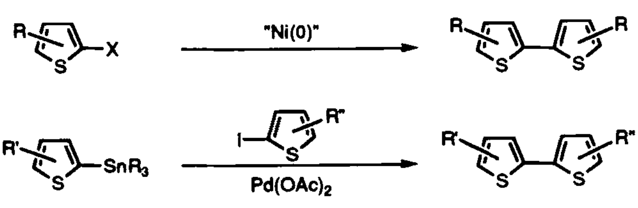
The syntheses, structures, properties, and reactions of the three bithiophenes (**10–12**), and their derivatives, were the subject of an excellent comprehensive review published in 1992 and covering the literature up



(**10**) (**11**) (**12**)

to 1989 [92CH(44)755]. Accordingly, only work carried out since then is mentioned here. This is an area of intense current activity, principally because of the relevance of 2,2′-bithiophene (**10**) to the important conducting polymer polythiophene, which has also been the subject of a recent review (92CRV711). Many natural products, some of which have useful biological activity, are derivatives of **10** (e.g., aphyllocladin, Fig. 1), and these, too, have been reviewed [85CH(44)261; 91FOR(56)87].

a. *Synthesis.* Although 2,2′-bithiophene (**10**) is now commercially available, there have been several new syntheses of this compound [89PS(46)153, 89SC307; 93HAC185, 93MI2; 94T11893]. Numerous derivatives of **10** have been prepared in recent years for the preparation of modified polythiophene polymers. Symmetrically substituted derivatives are best prepared (Scheme 6) by nickel-mediated homo-coupling reactions [91BCJ864; 90JOC3091;



SCHEME 6

95TL665] or other self-coupling reactions [95JA2467, 94TL815]. Unsymmetrically substituted derivatives have been made by Stille cross-couplings (Scheme 6) [92MM1901; 94MM3039, 94T11249; 95JCS(P1)537], by Suzuki couplings [90PS(48)239], by other cross-couplings [89PS(42)63; 91BCJ864; 94BCJ2187; 95JOC8363], and by procedures involving thiophene ring formations (94JOC4350, 94TL9387). There has been considerable interest in solvatochromic derivatives of **10** containing an electron donor substituent in one ring and an electron acceptor in the other [93AGE719; 95JCS(P2)171, 95JOC2082]; such compounds are made by palladium-catalyzed coupling reactions and show strong conjugation between the two rings.

The other two isomers, **11** and **12,** have been less studied since the previous review [92CH(44)755]. Several derivatives of **11** have been made by cross-couplings [90H(30)303; 92TL2199] and by cyclization reactions (92T10377; 94JOC4350, 94TL9387). Extensions of the procedures just discussed have been used to prepare many oligothiophenes [91S462; 92H(34)1487, 92MI4; 93JA8716, 93JCS(P2)489; 95JOC6813].

b. *Physical Studies.* The structural features of **10** and its derivatives have been the focus of much current research, again because of the relevance to polythiophene. As described in the previous review [92CH(44)-755], an early crystal structure determination of **10** was somewhat imprecise because of decomposition of the crystals during data collection [68AX(B)467]. Recent low-temperature X-ray crystal structure determinations have resolved this problem. At 173 K, the structure was interpreted in terms of disordered planar structures composed of 85% transoid conformations and 15% cisoid [94AX(C)1941], whereas at 133 K the transoid planar structure showed no evidence of disorder [94AX(C)1942]. The X-ray crystal structures of many substituted derivatives of **10** have also been reported [88AX(B)509, 88AX(C)562, 88AX(C)1800; 89CS221, 89JST(196)171; 92JCS(CC)1137, 92JCS(P2)761, 93ACS184, 93AGE719, 93JOC3091, 93MI3, 93T3735, 93ZK(208)145, 93ZK(208)148; 94AGE739, 94JOC442, 94TL3957; 95AX(C)690], as well as those of many oligothiophenes [88H(27)1391; 91MI2; 92MI2; 93JA12158, 93SM(60)239; 94AX(C)1112]. In general, such structures are usually in planar transoid conformations, a notable exception being the 5-formyl derivative, which is cisoid [94AX(C)1945]. However, substitution in the 3 (and 3′) position(s) hinders coplanarity, except in the case of alkoxy substituents that also have planar transoid structures [94MI2; 95AX(C)1394, 95JA9832]. Such features have important consequences for the properties of the corresponding polymers. X-ray crystal structures have also been reported of some derivatives of **12** [91AX(C)596; 92JCS(P2)1839; 93CL533;

94JOC442, 94TL1977], which, unless structurally constrained to planarity, are generally nonplanar.

Theoretical calculations of the structure and conformation of **10** appear regularly [89JCC635; 90JPC5761; 92JST(259)181, 92PJC1487; 93IZV869, 93JPC3504; 94JCP(101)1369, 94JPC9450; 95JCP(102)3580, 95JPC4955, 95JST(330)223]. The latest and most reliable of these show that the potential energy surface for rotation about the inter-ring bond is relatively flat, and generally agree that there are two nonequivalent, slightly nonplanar energy minima. These results are in agreement with a recent gas-phase electron diffraction study, which showed two conformations in a ratio of 56:44 with torsional angles of 148° and 36°, respectively [93SM(59)259].

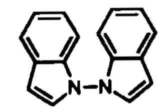
Many other physico-chemical studies of **10** have been reported since the previous review. These include NMR studies [90ZOR392; 93MP(80)-177; 94JST(323)181], electronic absorption and emission spectroscopy [90PS(48)239; 91JCP(95)4783; 93IJC(B)766, 93IZV869, 93SM(60)23; 94JPC3631, 94JPC4990; 95JCP(102)3580, 95PAC9], vibrational spectroscopy (94JCC405), and electrochemical measurements [89KGS1213; 90PS(48)239; 91MI3; 93JPC513]. The effects of substituents on many of these properties have also been studied [95JCS(CC)881]. Photoelectron spectra have been reported for all three isomeric bithiophenes (**10–12**) (91JPO675).

c. *Reactions.* The reaction chemistry of **10** has been well studied. As expected, it is most reactive in the 5 (and 5′) position(s), where it readily reacts with electrophiles, free radicals, and metallating agents. Halogenation reactions have been studied in detail, and recent advances have allowed selective preparations of variously substituted halo derivatives of **10** [91BCJ2566, 91H(32)1805; 92JCR(S)350; 93S1099; 95JA2467]. Formylation reactions have been much studied [90SL29; 95TL665], and the products used for the preparations of larger species, such as annulenes (93M931; 94JOC807). Friedel–Crafts acylations of **10** have been reported, en route to the preparations of oligothiophenes (91S462). New methods of alkylations of **10** have been described [89JHC533; 91H(32)1805; 93JOC3091). Derivatives of **10** with various heteroatom [90AGE655; 93JOC3091; 94SM(62)233] and metal [92JOM(429)403, 92TL405] substituents have also been synthesized. 2,2′-Bithiophene (**10**) is dimerized by tetrachloropalladate [91JOM(406)C29], while Birch reduction of substituted derivatives gives monocyclic compounds (93G527). Ring-opening reactions have been used to convert **10** into isotopically labeled palmitic acids (93T6613). Both **10** and **11** have been converted to S,C-ylids by rhodium-acetate-catalyzed reactions with dimethyl diazomalonate (89CS221).

D. Benzo Derivatives

1. *Biindoles, Biisoindoles, Bicarbazole*

a. *Biindoles—Synthesis.* There are six isomeric biindoles (**13–18**) linked through the five-membered rings. None of the parent N-linked isomers (**13–15**) is known. Substituted derivatives of **13** have been prepared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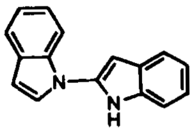
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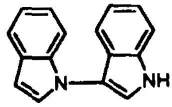
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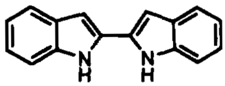
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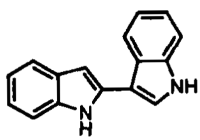
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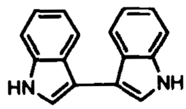
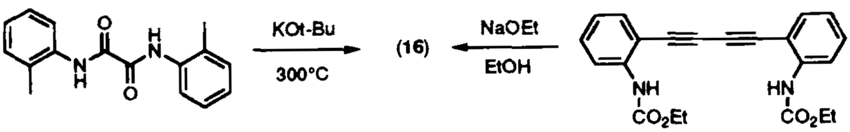

(18)

by permanganate oxidation of indoles (72CJC3397) and by reduction of 1-hydroxyindoles [68JCS(C)1243]. Substituted derivatives of **14** have recently been prepared by substitution reactions involving indole as the nucleophile [92S731; 94H(38)273]. The simplest known derivative of **15** is a naturally occurring hexabromo derivative of marine origin (82JA3628).

In contrast, all three C–C linked isomers (**16–18**) are well-studied compounds that have been synthesized by a variety of methods. 2,2′-Biindole (**16**) was first prepared, in poor yield, by a double Madelung cyclization [12CB1128; 14LA(405)58]. This procedure has undergone modifications (44CB788; 57JCS4141) and has recently been optimized (Scheme 7), so it is still the method of choice [95T5631]. More recent preparations of **16** include copper-promoted couplings of 2-tributylstannylindole [95TL283] and N-protected 2-lithioindoles [80T1439; 92H(34)1285]; a



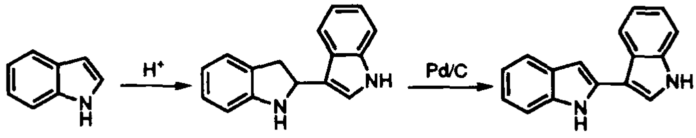
Scheme 7

procedure employing a double intramolecular Wittig reaction (88CB2259); a palladium-catalyzed coupling of *N,N'*-carbonylindole (80T1439); a Stille coupling (95JOC6218); and a high-yielding five-step synthesis, culminating in the double cyclization of a diyne (Scheme 7) (95SL859).

Symmetrical and unsymmetrical substituted derivatives of **16** have been prepared by extensions of these procedures (89T6427) and by other miscellaneous methods [81H(16)1441; 82JCS(CC)977; 84JCS(CC)441; 85-JCS(CC)1174; 93HCA2356; 94SC1701]. Whereas indole itself undergoes acid-catalyzed dimerization to give a dihydro derivative of **17** (see later discussion), 3-substituted indoles (e.g., skatole) dimerize to dihydro derivatives of **16,** which can be oxidized to the corresponding 2,2'-biindoles (60TL13). 3,3'-Bridged derivatives of **16** are readily prepared by double Fischer cyclizations of cyclic α-diketone bisphenylhydrazones (58JCS1525; 69CB1198; 89JOC1720). 2,2'-Biindole has also been incorporated as a subunit into macrocyclic ligands [85JCS(CC)1174].

2,2'-Biindoles are found in many naturally occurring compounds. For example, a tetrabromo derivative has been isolated as a marine natural product (82JA3628), while derivatives, oxygenated in the benzo rings, are intermediates in eumelanin biosynthesis (85TL2805). It is also a subunit in the much-studied, biologically active indolo[2,3-a]carbazole alkaloids [87CS539, 87FOR(51)1; 88MI1; 93MI4; 94JHC377; 95JA552, 95TL7841, 95TL8383]. However, by far the most studied derivatives relate to indigo, which, along with its 6,6'-dibromo derivative (Tyrian purple), has been used in dyeing since ancient times. Although the chemistry of such compounds is considered beyond the scope of the present review, it should be noted that the 3,3'-dihydroxy derivative of **16** is the colorless, reduced form (leucoindigo) that on oxidation produces indigo [54CH(8)-171]. Accordingly, very many 3,3'-dioxygenated derivatives of **16,** in various oxidation states, have been synthesized. 3-Oxygenated derivatives of **16** have also recently been shown to possess useful biological activity (94BMCL1771).

2,3'-Biindole (**17**) has also been prepared by several methods. It was first made by reduction of the 3-hydroxy derivative (indoxyl-red) (44CB788), but this reaction appears to be somewhat capricious (63JOC418). It can be prepared directly from indole by various methods (73JHC121; 76LA1039), the simplest of which would seem to be by catalytic dehydrogenation of the 2,3-dihydro derivative (Scheme 8) (62JOC507), which, in turn, is readily obtained by acid-catalyzed dimerization of indole [57JCS3544; 63AHC(2)287]. Other preparations of **17** include a Stille coupling of N-protected precursors (93HCA2356); dehalogenation, via a Grignard intermediate, of the 2'-chloro derivative (77JHC1123); a Fischer cyclization of 3-acetylindole (70JIC123); and an acid-catalyzed reaction between indole



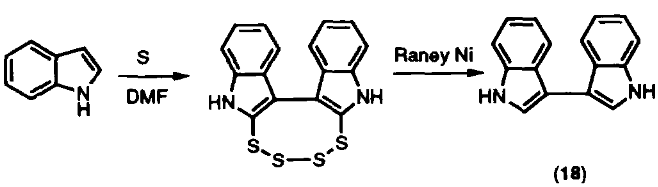
(17)

SCHEME 8

and 3-bromoindole [83JCS(CC)1074; 84T3251; 86T5019]. Substituted derivatives of **17** have been prepared by various cyclization or coupling methods [62JOC507; 64JOC2030; 80T1445; 84JCS(CC)441]. Oxygenated derivatives have been much studied as analogues of indigo (the indirubins).

3,3′-Biindole (**18**) was first prepared by Gabriel via a circuitous route involving decarboxylation of carboxylic acid derivatives (23CB1024). It has subsequently been prepared by reaction between indole and indoxyl (44CB788); by a Fischer cyclization [78IJC(B)1122]; by sulfuration of oxindole (67CIL275; 69CPB550); by deselenation of 3,3′-diindolyl selenide (68ACS1883); by degradation of an indole trimer (80T1445); and from a dinitrostyrene, via coupling of a radical anion (91BCJ1787). Although early reports (39G562; 42G549; 57JCS4141) that **18** is readily prepared by heating indole with sulfur appear to be somewhat oversimplified (60JA2739; 76LA1039; 94TL1977), this does form the basis of a useful method of preparation (Scheme 9) by reduction of an intermediate tetrasulfide (60JA2739; 76LA1039). Another efficient method of preparation is by lithium aluminium hydride reduction of the product of reaction of indole with isatin (71ACS1277).

Substituted derivatives of **18** have also been prepared by a variety of methods, including acid-catalyzed rearrangements of indolines (92JHC-1349), double Fischer cyclizations (64CJC2900), metal-catalyzed coupling reactions [86JCS(P1)2305; 94TL793], and ring contraction of 2-azidoquinoline N-oxides [73H(1)227; 80JOC5316]. Again, oxygenated derivatives have been much studied as indigo analogues (the isoindigos). Halogenated derivatives have also been isolated as marine natural products (89T7301; 91JNP1661).



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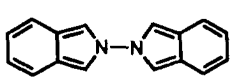
SCHEME 9

b. *Biindoles—Physical Studies.* There have been no reported X-ray crystal structures of unsubstituted biindoles. Reports have described the structures of the 1,1′-dimethyl derivative of **16** (94JHC377) and a 3,3′-bridged derivative (95JHC1335). The only reported structures of derivatives of **17** are of pentacyclic compounds wherein **17** is bridged, in various positions, between the two ring systems [89MI1; 92AX(C)382; 93CB1835]. The structures of a tetrasubstituted derivative of **18** [92JCR(S)222] and of a hexasubstituted marine natural product (89T7301) have been published, as has a cyclic bisdisulfide that contains **18** as subunits (94TL1977).

c. *Biindoles—Reactions.* Reaction chemistry has been reported for all three known biindoles. Following very early reports [14LA(405)58; 16CB2039] of electrophilic substitution reactions of **16,** its chemistry was almost totally ignored [72JCS(P1)418; 80T1439] until recently, when there have been numerous reports of the reactions of **16** [92H(34)1285; 93TL5329; 95TL2477, 95T12797], and its 1,1′-dimethyl derivative [92AP353; 94H(38)2267; 95JHC1335; 94JHC377], with various dienophiles. These later studies have been principally directed toward the synthesis of the indolo[2,3-*a*]carbazole alkaloids and have shown that **16** undergoes both Diels–Alder reactions and Michael addition reactions.

Reported reactions of the 2,3′-isomer (**17**) include its nitrosation [33LA(504)1]; formylation (80T2505); methylation (76LA1039) and subsequent nitrosation to a pentacyclic compound [77JCS(P1)1024]; reaction with a hydroxyindole (80T1445); and its electropolymerization (94CM-1742). The 3,3′-isomer (**18**) undergoes acid-catalyzed rearrangement to **17** (23CB1024); is oxidized by various reagents to a dehydro derivative [57JCS4141; 76ACS(B)853, 76LA1039]; and undergoes electropolymerization (94CM1742).

d. *Biisoindoles.* None of the unsubstituted biisoindoles (**19**–**21**) is known. However, each of these skeletons is present in known oxidized,



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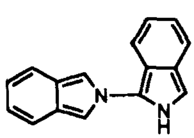

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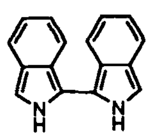

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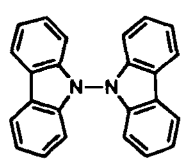


(22)

oxygenated derivatives, such as *N,N′*-biphthalimide, which are beyond the scope of the present review [1872LA(164)229; 37JCS16; 48BSF889; 78AX(B)3477].

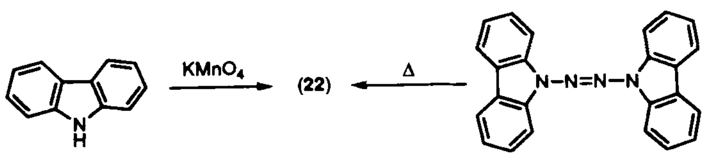
e. *Bicarbazole—Synthesis.* 9,9′-Bicarbazole (**22**) is a well-studied compound. It is best prepared by the original procedure (Scheme 10) involving permanganate oxidation of carbazole (21JCS216; 27JCS1214), and this has been extended to substituted derivatives (27JCS1214; 57CCC64; 72CB2694). Carbazole is also oxidized to **22** by silver oxide (20JA2405), by nickel peroxide (67NKZ659), and by photooxidation (81JOC1496; 84TL5363). Contrary to a very early report [12LA(392)169], **22** can also be prepared (Scheme 10), along with isomers, by thermolysis of *N,N′*-azocarbazole [68JCS(C)740].

f. *Bicarbazole—Physical Studies.* The X-ray crystal structure of **22** has been reported [93JCS(P2)757] and showed two ring systems inclined to one another at an angle of 70.0°. This conformation was reproduced by AM1 semiempirical calculations, but not by MM3 molecular mechanics calculations [93JCS(P2)757]. There have been many spectroscopic studies of **22.** These include investigations of NMR spectra [71AJC2293; 88MRC1109; 93JCS(P2)757], mass spectra (71CB808), electronic spectra (67NKZ463; 84MI1), infrared and Raman spectra [85JST(131)233], photoelectron spectra (83MI1), and fluorescence spectra (84MI2). Much of this work has centered on deducing the conformation of the molecule (70JPC227).

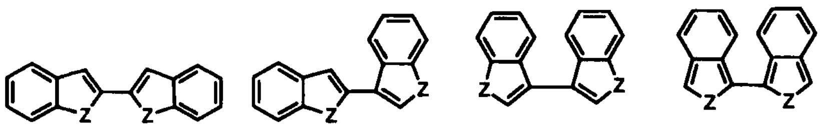
g. *Bicarbazole—Reactions.* Some reaction chemistry has been described for **22,** which can be halogenated to tetrahalo derivatives (27JCS1214) and reduced to carbazole (27JCS1214). There have been several studies of the photolysis of **22** [69JPC4315; 75DOK(224)616; 78MI1], which produces the 9-carbazolyl radical, whereas thermolysis results in rearrangement to two C–N linked isomers (72CJC3397). 9,9′-Bicarbazole also undergoes electropolymerization [81JEC(129)229].

2. *Bibenzofurans, Biisobenzofuran*

Of the three possible isomeric bibenzofurans (**23**–**25**) only the 2,2′-isomer (**23**) is known. It was first prepared by a double cyclization, as shown in Scheme 11 (59BCJ514; 60BCJ223), and has subsequently been prepared by a base-catalyzed single cyclization of a salicaldehyde ether (74LA523);



SCHEME 10



(23) Z = O (27) Z = S

(24) Z = O (28) Z = S

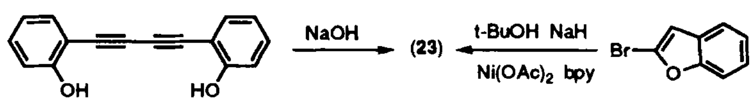
(25) Z = O (29) Z = S

(26) Z = O (30) Z = S

by palladium-catalyzed homo-couplings of benzofuran (73BCJ1220) and of 2-(chloromercury)benzofuran (74MI2); as a by-product in an attempted copper-catalyzed cross-coupling of 2-iodobenzofuran (91T7981); by a copper-induced homo-coupling of 2-trimethylstannylbenzofuran [95TL283]; and, most conveniently (Scheme 11), by nickel-mediated homocoupling of 2-bromobenzofuran (94T11893). Substituted derivatives of **23** have been prepared by extensions of these procedures (72CB1943; 86JHC1277). Although the 2,3'-isomer (**24**) has not been prepared, 3-oxygenated derivatives have long been known to result from the condensative dimerization of cumaranones (10CB212; 55JOC813). The 3-acetoxy derivative undergoes an interesting acid-catalyzed transformation to a cyclic tetramer (78TL3143). Substituted dihydro derivatives of **24** have been reported to result from acid-catalyzed dimerizations of methylbenzofurans (70NKZ753). Oxidized derivatives of both **23** and **24** have been much studied as analogues of indigo (oxindigos and oxindirubins, respectively). 1,1'-Biisobenzofuran (**26**) is not known, but this skeleton is present, in an oxidized form, in biphthalide [1872LA(164)229; 61JA173] and the product of base-catalyzed self-condensation of phthalide (64JOC3070). There have been no structural or reaction studies of the parent bibenzofurans.

3. *Bibenzothiophenes*

a. *Synthesis.* All three bibenzo[*b*]thiophenes (**27**–**29**) are known. The 2,2'-isomer (**27**) was first prepared by a lengthy procedure involving nitro- and amino-substituted derivatives [29LA(470)1]. It has commonly been prepared (Scheme 12) by oxidative coupling of 2-lithiobenzothiophene (52JA664; 57MI1; 59MI1), and this has been extended to substituted derivatives (65NKZ102, 65NKZ1067; 68NKZ192). It can also be prepared by



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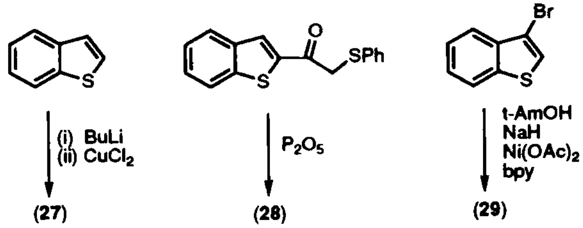


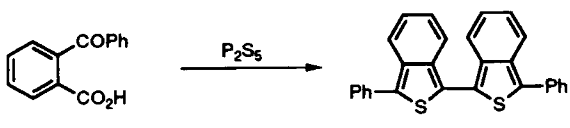
SCHEME 12

acid-catalyzed dimerization of benzothiophene [80JCS(P1)677], a process that had earlier been used to prepare substituted derivatives (70BSF3523). The most recent preparation is a high-yielding homo-coupling of 2-bromobenzothiophene, mediated by liganded nickel complex reducing agents (94T11893).

2,3′-Bibenzo[*b*]thiophene (**28**) was also first prepared by a lengthy synthesis [29LA(470)1] and subsequently (Scheme 12) by a dehydrative cyclization, with formation of the 3-substituted ring (59MI1). 3-Oxygenated derivatives of **28** are readily available by acid-catalyzed dimerization of 3-hydroxybenzothiophenes [28LA(462)46; 49LA(563)15; 86CS287, 86T763]. Oxygenated derivatives of both **27** and **28** have been much studied as indigo-type dyes, these being the thioindigos and thioindirubins, respectively (45JCS893; 64ZPK1165; 71KKZ440). 3,3′-Bibenzo[*b*]thiophene (**29**) was first prepared by an Ullmann coupling of 3-iodobenzothiophene (58JOC206); it has since been made by a cyclization reaction analogous to that shown in Scheme 12 for the formation of **28** (59MI1). Most commonly, **29** is made from 3-bromobenzothiophene by metal–halogen exchange and oxidative coupling of the resultant anion (59MI1; 73JOC2814; 75AGE713), or, more directly (Scheme 12), by liganded nickel-mediated coupling (94T11893). All three isomers (**27**–**29**) have been detected from aquathermolysis of benzothiophene (92EF431).

1,1′-Bibenzo[*c*]thiophene (**30**) has not been reported. The simplest derivative is the 3,3′-diphenyl derivative, which was prepared as shown in Scheme 13 and desulfurized with Raney nickel (64JOC2019).

b. *Physical Studies.* There have been relatively few structural and spectroscopic studies of the bibenzo[*b*]thiophenes. In association with photo-



SCHEME 13

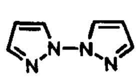
electron studies of **27** and **28**, theoretical calculations have been carried out on the conformations of these two compounds [92JST(265)119], which have also been the subject of photoluminescence studies [85ZN(A)497]. In connection with studies of polyisobenzothiophene (84JOC3382), there have been several theoretical calculations of the electronic properties of **30**, as a model for the polymer (87IJQ163, 87MM2023; 88MI2).

c. *Reactions.* The reaction chemistry of these compounds has received some attention. The 2,2′-isomer (**27**) has been desulfurized with Raney nickel to 1,4-diphenylbutane (57MI1). Reaction of **27** with elemental sulfur yields the 3,3′-sulfide bridged derivative, which also forms 1,4-diphenylbutane upon desulfurization (59MI2). The 3,3′-disulfide bridged derivative of **27** has recently been reduced to the corresponding dithiol (94CB401). The reactions of **28** and **29** with sulfur have also been reported (61MI1), as have Diels–Alder reactions of **27** and **28** with maleic anhydride (77CZ507). The 3,3′-isomer has been dilithiated in the 2,2′-positions and the resultant compound dimerized to a cyclic tetramer (75AGE713) and diformylated for conversion to heterohelicenes (73JOC2814). A cyclic tetramer has also been made from **27** (78CB1330).

III. Five-Membered Rings: Two Heteroatoms

A. Bipyrazoles

a. *Synthesis.* There are six isomeric unsubstituted bipyrazoles (**31**–**36**). Since some of these exist as nonidentical tautomers,[1] there are in fact 10 different individual tautomers of bipyrazoles, and hence 10 possible structures for (nontautomeric) N-substituted derivatives. Despite attempts



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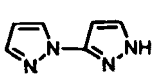

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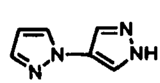

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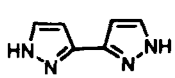

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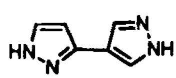

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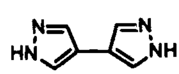
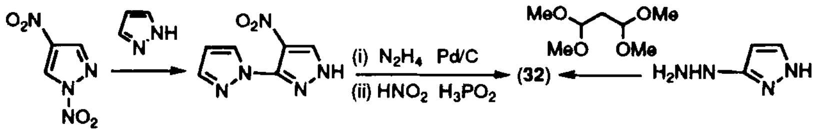


(36)

[1] Throughout this review all compounds that can exist as two, or more, tautomers are represented in the structural diagrams as 1-H tautomers. This is not intended to imply that this is the most stable tautomer; in many cases the relative stabilities are not known (76AHCS1).



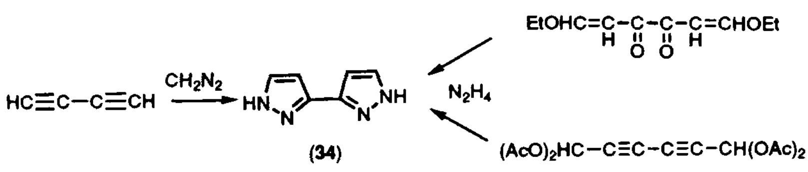
SCHEME 14

at rational synthesis (86T2377), 1,1′-bipyrazole (**31**) has only been tentatively assigned as a minor product resulting from the flash vacuum pyrolysis of tris(pyrazol-1-yl)methane (88T6429). Stable substituted derivatives are known [85H(23)2619].

1,3′(5′)-Bipyrazole (**32**) was first prepared (79JOC4156), as shown in Scheme 14, by a sequence involving a cine-substitution of 1,4-dinitropyrazole by pyrazole and subsequent removal of the 4′-nitro group. It has since been prepared by the more obvious route (Scheme 14) of condensing 3(5)-hydrazinopyrazole with malondialdehyde (85TL5485). Various derivatives have been prepared by similar condensations (79JOC4156; 83JHC277). The 4,4′-dimethyl derivative was obtained from the bromination of 4-methylpyrazole [55LA(593)179] and the 4,4′-dichloro derivative from the chlorination of silver pyrazolate (70CB1942). Other derivatives have been obtained by dehydrogenation of pyrazolylpyrazolines [68DOK(179)337].

1,4′-Bipyrazole (**33**) is not known. The simplest known derivative is the 4-nitro compound, which was obtained by condensation of 1-(diformylmethyl)-4-nitropyrazole with hydrazine (86IZV2392; 88CCC1529). Other more highly substituted derivatives are known (93FA949).

3,3′-Bipyrazole (**34**) has been prepared by a number of methods (Scheme 15). It was first prepared (Scheme 15) from the very slow reaction of diacetylene with diazomethane [41LA(549)279] and was subsequently made from a dimethyl derivative, the methyl groups being removed by oxidation and decarboxylation (46G223). Later, more direct, syntheses (Scheme 15) involve the condensation of logical precursors with hydrazine (65CB2260; 78M337). It has also been prepared, via the 4,4′-dicarboxylic acid, in a multistep process from a naphthoquinone dimer (67CB2885) and from pyrazolines obtained by reaction of diazomethane with butadiene and vinyl-



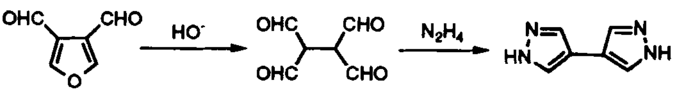
SCHEME 15

acetylene (68CB3700). Many substituted derivatives have been synthesized by condensation chemistry; indeed, such compounds have been known for more than a century [1894LA(278)295; 46G223; 55JCS1205; 58JCS2486; 72JHC1373]. Other incidental methods yielding substituted derivatives of **34** include preparations from isoxazoles (46G223; 71JHC1035), pyrazolines (84KGS226), and a diazepine (58JCS4094), and by the reaction of the dilithio derivative of acetophenone phenylhydrazone with diethyl oxalate (75JHC1159).

3(5),4′-Bipyrazole (**35**) has not been reported. The simplest known derivatives are the two isomeric *N,N′*-dimethyl derivatives, which were prepared as part of a study of all six possible 1,1′-dimethylbipyrazoles (72JHC1373). Diphenyl (52JA3243), trimethyl (79AP863), and triphenyl (59JCS1819) derivatives have also been prepared.

4,4′-Bipyrazole (**36**) has been prepared by condensation of hydrazine with a tetraaldehyde (Scheme 16), which is readily available from base hydrolysis of furan-3,4-dicarbaldehyde (64JOC3046). A tetramethyl derivative has been prepared by a similar condensation (72JHC1373; 82TMC234). The 1,1′-diphenyl derivative has been prepared by coupling of the corresponding Grignard reagent [68JCS(C)466; 69JCS(C)1515] and by an unusual sequence that begins with a dipolar addition to 1-methylpyrrole (72TL4703). The 3,3′-diphenyl derivative has been made from the bis(tosylhydrazone) of an ethylenic 1,5-dialdehyde (94BSF48). Another highly substituted derivative was made by Ullmann coupling of a substituted 4-bromopyrazole (71JHC153).

b. *Physical Studies.* The only X-ray structure of an unsubstituted bipyrazole is that reported for the 3,3′-isomer (**34**), which showed a planar transoid structure, with the molecules forming zigzag chains held together by intermolecular hydrogen bonds [94SA(A)727]. The 1,1′-isomer has been the subject of MNDO calculations (84CJC687), whereas various isomers have been studied by NMR methods [79JOC4156; 85H(23)2629; 87T4663; 94SA(A)727]. Basicity measurements have been reported for methyl-substituted derivatives of **32** and **34** (89JHC893).



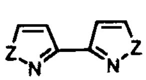
(**36**)

SCHEME 16

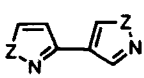
c. *Reactions.* *N*-Alkylation reactions have been reported for **32** (85TL5485) and derivatives (80JHC137), and for **36** (85CPB2535). As is usual for pyrazoles, electrophilic substitution reactions occur, where possible, in the 4 position; for example, derivatives of **34** and **35** undergo bromination and formylation reactions in this position (59JCS1819; 64G1183; 75JHC1159). A tetramethyl derivative of **36** has been used to prepare an unusual dimeric paraionic compound (82JOC295). Bipyrazoles have also been incorporated as structural motifs in larger molecular species: **31** has been incorporated into cryptands [85JCS(CC)1765], **32** into macrocycles (81T987), including chiral examples (93MI5), and **34** into macrocycles and crowns (84BSF473; 93MI6). The coordination chemistry of the 3,3′, 5,5′-tetramethyl derivative of **36** has been extensively studied, and this has provided some interesting multinuclear complexes [82TMC234; 84ICA-(81)99; 92JCS(CC)1726].

B. Biisoxazoles

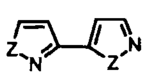
a. *Synthesis.* The study of biisoxazoles has been extensive over the past 40 years, with Italian workers being particularly active in the area. There are six possible biisoxazoles (**37**–**42**). Synthetic approaches utilize the standard



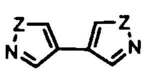
(**37**) Z = O
(**43**) Z = S



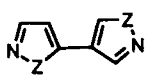
(**38**) Z = O
(**44**) Z = S



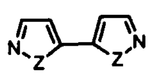
(**39**) Z = O
(**45**) Z = S



(**40**) Z = O
(**46**) Z = S



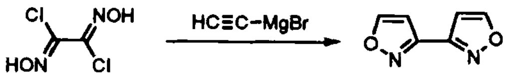
(**41**) Z = O
(**47**) Z = S



(**42**) Z = O
(**48**) Z = S

methods for construction of isoxazole rings. Substituted derivatives of **37**, **39**, and **42** have been known for some time (40G676, 40G685; 42G242).

The 3,3′-isomer (**37**) was first prepared (Scheme 17), along with 5,5′-disubstituted derivatives, by reaction of dichloroglyoxime with acetylenic Grignard reagents (57G638) with formation of both isoxazole rings. It was subsequently made by an analogous reaction from a preformed isoxazole precursor (59G587), and this procedure was extended to the preparation of higher oligoisoxazoles (59T24; 60G1253). It can also be prepared, in



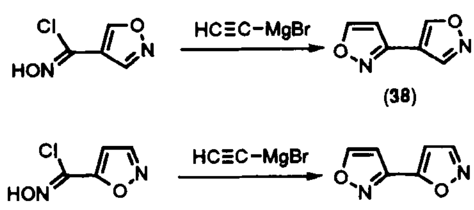
(37)

SCHEME 17

high yield, from exclusively gaseous reactants, by reaction of acetylene with a mixture of nitric oxide and nitrogen dioxide absorbed in warm ethyl acetate under pressure (61JOC2976). Substituted derivatives have been prepared by reaction of cyanogen *N,N'*-dioxide with acetylenes [63AGE260; 65LA(687)191] or, in a more recent variant, with trimethylsilyl enol ethers (87JHC337).

3,4'-Biisoxazole (**38**) and 3,5'-biisoxazole (**39**) were each prepared (Scheme 18) by reaction of ethynyl magnesium bromide with the appropriate isoxazole hydroximic chloride (59MI3; 66G443), each of which was prepared by multistep procedures. Although neither 4,4'-biisoxazole (**40**) nor 4,5'-biisoxazole (**41**) has been prepared, simple substituted derivatives are known. The tetramethyl and tetraphenyl derivatives of **40** were formed, in modest yields, by reaction of hydroxylamine with the appropriate tetraketone (64G393); this method has been extended to less symmetrically substituted derivatives (77CCA527; 84LA199). The tetramethyl derivative was also obtained from the homo-coupling of the corresponding Grignard reagent [80JOM(195)275]. Di- and trisubstituted derivatives of **41** have been made by multistep procedures involving hydroxylamine condensations for the construction of one ring and a nitrile oxide addition for formation of the second isoxazole [65AC(R)1233; 66RS986]. The 3'-methyl derivative of **41** has been made from 3,5-dimethylisoxazole by sequential treatment with the Vilsmeier–Haack reagent and hydroxylamine (71MI1).

The 5,5'-isomer (**42**) has been synthesized by reaction of protected 2,4-hexanediyne dialdehydes with hydroxylamine (58T359; 78M337) and by reaction of fulminic acid with diacetylene (59MI4) (Scheme 19). The latter



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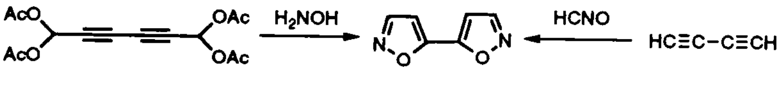
(39)

SCHEME 18



(42)

SCHEME 19

reaction has been adapted for the preparation of the tetradeuterated derivative (64RS567) and 3,3′-disubstituted derivatives (59G598). The 3,3′-dimethyl derivative has also been made by cyclization of a tetraketone dioxime (90IZV2069).

b. *Physical Studies.* X-ray crystal structures have been reported for all four known parent biisoxazoles. The 3,3′-isomer (**37**) [67ZK(124)143] and 5,5′-isomer (**42**) [68ZK(127)388] have very similar planar, transoid structures, whereas the 3,4′-isomer (**38**) [69AX(B)730] has a small twist about the inter-ring bond. The 3,5′-isomer (**39**) (68MI1) is disordered, but the molecular packing was interpreted to indicate a cisoid structure. The 5,5′-isomer (**42**) has been the subject of several theoretical and spectroscopic investigations (70TCA327, 70TFS563, 70TFS572), all of which indicated a planar, transoid structure. Analyses of the NMR spectra, in nematic phases, of both the 3,3′ and 5,5′ isomers have been reported [71CPL(8)421; 72JCP(56)1290].

c. *Reactions.* Very little reaction chemistry has been reported for this class of compounds. The 3,3′-, 3,5′-, and 5,5′-isomers have been brominated and nitrated and, as expected, substitution occurs in the 4- and 4′- positions (59MI5). The 5,5′-isomer (**42**) undergoes base-catalyzed ring opening (58T359), a common reaction of isoxazoles. Substituted derivatives of **41** have twice been reported to undergo hydrogenolysis with ring opening, followed by ring closure to 4-pyridones (71T379; 86AP242).

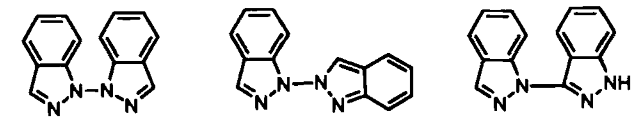
C. BIISOTHIAZOLES

In contrast to the numerous reports of biisoxazoles, none of the six possible biisothiazoles (**43**–**48**), or even a simple substituted derivative, is known. This is presumably a consequence of the instability or lack of availability of the sulfur analogues of hydroxylamine [78JCS(D)277] and nitrile oxides (80JOC3753), from which biisoxazoles are commonly constructed.

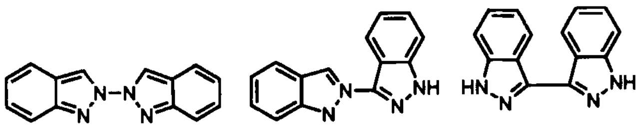
D. Benzo Derivatives

1. *Biindazoles*

There are six possible isomeric biindazoles (**49–54**) linked between the five-membered rings. Only two of the parent compounds (**52** and **54**) are known. Two highly substituted derivatives of 1,3′-biindazole (**51**) have been

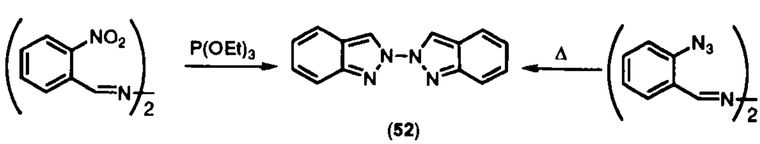


(**49**) (**50**) (**51**)

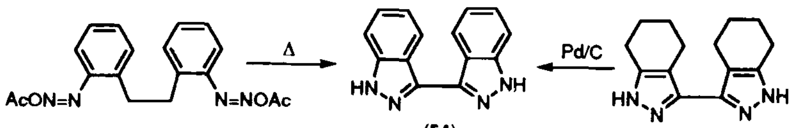


(**52**) (**53**) (**54**)

reported as minor products from reactions of nitroindazoles and both seem to result from cine-substitution processes (85PHA105; 88JOC2055). The 2,2′-isomer (**52**) is readily prepared by double nitrene insertion reactions. Thus, triethyl phosphite reduction of *o*-nitrobenzaldehyde azine (65JCS4831) or, better, thermal decomposition of *o*-azidobenzaldehyde azine (64JOC1150) leads to good yields of **52** (Scheme 20). This procedure has been extended to the synthesis of a number of substituted derivatives, including the incorporation of the 2,2′-biindazolyl moiety into crowns and cryptands (88JOC2055). The 6,6′-dinitro derivative of **52** had earlier been reported to result from reaction of 6-nitroanthranil with hydrazine hydrate (61JOC8714); however, this report appears to be erroneous, although 7-nitroanthranils do, in fact, undergo this reaction (77JOC897), which proceeds via a furoxan (80JOC1653). An aromatic derivative of **52** containing a 3,3′-ethenyl bridge has also been prepared (88TL4315) and undergoes a



SCHEME 20



(54)

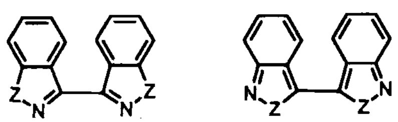
SCHEME 21

photoinduced electrocyclic ring opening with cleavage of the central N—N bond. The ^1H and ^{13}C NMR spectra of **52** have been fully assigned (88JOC2055). Palladium complexes of three dimethyl derivatives of **52** have been studied [91JOM(410)257]; the ligands act in a chelating manner.

The 3,3′-isomer (**54**) has been prepared by two routes (71JOC1563) (Scheme 21): cyclization of bibenzyl-2,2′-bisdiazoacetate and dehydrogenation of an octahydro derivative made, in two steps, from cyclohexanone. A 1,1′-diaryl derivative of **54** had previously been prepared, with formation of one indazole ring, by oxidation of a benzoylarylhydrazone with lead tetraacetate and treatment with a Lewis acid [66JCS(C)1527]. Lead tetraacetate oxidation of **54** leads to $\Delta^{3,3'}$-bi-3H-indazole (71JOC1563).

2. *Bibenzisoxazoles, Bibenzisothiazoles*

Neither of the parent bibenzisoxazoles, **55** or **56,** is known. A highly substituted derivative of 3,3′-bi-1,2-benzisoxazole (**55**) was reported to be formed, in low yield, from the chlorination of *p*-dimethylaminobenzaldehyde oxime (71JOC2146). Related molecules are known in which the benzo groups are present as tetrahydro analogues; such an octahydro derivative of **55** is produced by reaction of cyanogen dioxide with the trimethylsilyl enol ether of cyclohexanone (87JHC337). The corresponding octahydro derivative of **56** is formed by reaction of diethyl oxalate with the C(α),O-dilithio derivative of cyclohexanone oxime (75JHC1159).



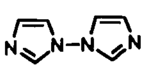
(55) Z = O
(57) Z = S

(56) Z = O
(58) Z = S

Of the two sulfur analogues, 3,3′-bi-1,2-benzisothiazole (**57**) was long ago reported to result from the zinc reduction of 3-chloro-1,2-benzisothiazole, in unspecified yield (28CB1680). 3,3′-Bi-2,1-benzisothiazole (**58**) is not known, but dihydro derivatives have been reported to result from reactions of anthranilic acids with P_4S_{10} (69BSF1170).

E. Biimidazoles

a. *Synthesis.* There are six possible unsubstituted biimidazoles (**59–64**), although, like the bipyrazoles, some isomers exist as nonequivalent tautomers, and extra isomers are therefore possible for (nontautomeric) N-



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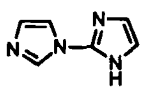

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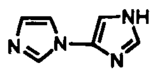

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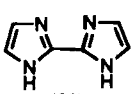

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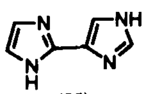

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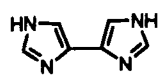
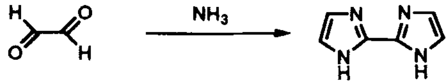


(64)

substituted derivatives. Although the unsubstituted parent 1,1′ isomer (**59**) is not known, numerous hexaaryl-substituted derivatives have been reported to be formed by oxidation of 2,4,5-triarylimidazoles (lophines). Such compounds have attracted much interest, particularly in the patent literature, because of their photochromic properties and applications in the photoimaging industry. However, many of the compounds reported are not actually derivatives of **59** but, in fact, 2,2′,4,4′,5,5′-hexaarylbi-1,2′-imidazoles, or mixtures of 1,2′-, 2,2′-, 1,4′- and 2,4′-biimidazoles. These compounds readily dissociate to stable 2,4,5-triarylimidazolyl free radicals, which recombine in a variety of isomeric ways [66JA3825; 70BCJ429; 72BCJ1474; 78CB1464; 84AHC(35)375]. The 2,4-dinitro-5-iodo derivative of **59** has recently been described (93JEM345).

Neither of the parent 1,2′ or 1,4′ isomers, **60** or **61**, is known. The 4′, 5′-dihydro derivative of **60** has been prepared (90S561), as well as di- and trisubstituted derivatives of **60** [79JOC4243; 82IJC(B)945; 89H(29)1325; 91IJC(B)399]. Other substituted derivatives of both **60** and **61** have been prepared for bioactivity screening [84IJC(B)342; 92MI3].

2,2′-Biimidazole (**62**) was the first reported biheterocycle. It was prepared in 1859 by Debus, who named it glycosine, by the action of ammonia on gloxal (Scheme 22) [1859LA(107)199]. This procedure has undergone



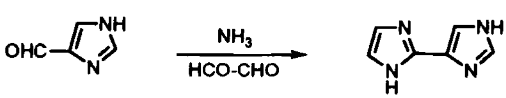
(62)

SCHEME 22

several refinements [57LA(605)32; 61JCS4790; 78IC2078; 87IC3569] and would still seem to be the most convenient method of preparation, despite the more recent publication of alternative procedures. These include the oxidation of N-protected biimidazolines (74S815) and the use of oxalimidic esters (86S336) or dibromoacetaldehyde (87KGS1069) as starting materials. Substituted derivatives can be prepared by related condensation reactions. For example, the 4,4′, 5,5′-tetramethyl and tetraphenyl derivatives have been prepared by mixed condensations from biacetyl or desylamine, respectively [57LA(605)32; 73CB2415]. The corresponding tetracyano derivative, which is not available from such a condensation, has been prepared by coupling 4,5-dicyanoimidazole with its 2-diazo derivative (82JA6155) and, more recently, by deprotection of N-substituted derivatives obtained by oxidative or Ullmann couplings of 2-lithioimidazoles or 2-bromoimidazoles, respectively (91JA6178). The 4-cyano and 4,4′-dicyano derivatives have been prepared from the corresponding trifluoromethyl compounds (86JOC3228). A large number of diversely substituted derivatives of **62** have been synthesized for screening of various types of bioactivity (75AF9; 90JMC317). The 2,2′-biimidazole subunit has also been incorporated into macrocycles (88IC4542), cryptands (92HCA1221; 93IC572), and polymers [88JPS(A)3015].

The synthesis (Scheme 23) of the parent 2,4′-isomer (**63**), along with a dimethyl derivative, has recently appeared in the patent literature (92JPP(K)4217669). The 4- and 5′-cyano derivatives have been prepared (90JMC317), as have other more highly substituted derivatives [75JMC895; 77AF1131; 89JCS(P1)95]. The parent 4,4′-isomer (**64**) has recently been prepared by the palladium-catalyzed coupling of a protected 4-iodoimidazole (Scheme 24) (94S681). A tetrasubstituted derivative has also been prepared by coupling of a lithioimidazole (92KGS61).

b. *Physical Studies.* Structural and spectroscopic studies of these compounds have been restricted to the 2,2′-isomer (**62**). The X-ray crystal



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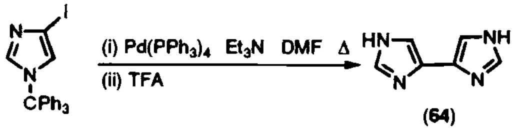
SCHEME 23



(64)

SCHEME 24

structure of **62** showed only a small twist (4.6°) about the inter-ring bond and that the molecules form ribbons held together by pairs of hydrogen bonds to each side of the molecule. [87AX(C)1435]. Structures have been reported for the tetranitro derivative, both as a dihydrate [90AX(C)1957] and as a diammonium salt [90AX(C)1959]; in both cases the structure is centrosymmetric, and hence the rings are strictly coplanar. This is not the case for N-substituted derivatives, such as the 1,1′-dimethyl-4,5′-dinitro derivative, which has a twist angle of 29.4° about the inter-ring bond [95AX(C)1414]. *Ab initio* molecular orbital calculations and molecular mechanics calculations have been performed on **62** [88JCS(P1)1975; 90IC1767] and assignments made of various spectroscopic parameters (76IC2681; 83IC3911; 88BSB731; 90IC167, 90IC1767, 90IZV2747). Basicity measurements have been reported for the 1,1′-dimethyl derivative (89JHC893).

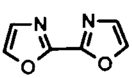
c. *Reactions.* The reaction chemistry of **62** has also been much studied. In a series of early papers by Lehmstedt, many alkylation, nitration, and halogenation reactions were reported, although the structural assignment of some of the products would appear to be questionable [27LA-(456)253; 33LA(507)213; 43CB879]. Halogenation of **62** normally produces the tetrahalo derivatives [43CB879; 57LA(605)32]; however, the mono- and dihalo derivatives have recently been prepared by employing the [2-(trimethylsilyl)ethoxy]methyl (SEM) protecting group (87JHC689). The same group has been used to control the selective lithiation of **62** for the introduction of formyl and methylthio substituents (86JOC1891). Mono- and disulfonations of **62** have been reported [64JPR(24)164], as has an unusual reaction with (dimethylamino)diethylborane, which led to an interesting fused-polycyclic compound that was characterized by X-ray crystallography (92IC3162). Many functional group interconversions of substituted derivatives of **62** have been reported (90JMC317). 1,1′-Dialkyl derivatives are readily prepared using a variety of alkylating reagents (43CB879; 86AP183; 88JHC1845). These include difunctional reagents that produce 1,1′-bridged derivatives (74JHC731; 89JOC3057) that can be further 3,3′-bridged to biimidazolium salts (89JOC3057; 95CB131). Reaction with acetylene (80IZV2339) gives *N*-vinyl derivatives that have been the subject of several studies (81ZOB892; 90IZV2747), including an X-ray structure determination (92IZV1376).

By far the most common use for **62** is as a chelating ligand in coordination chemistry [89CCR(93)205]. This ligand differs from 2,2′-bipyridine both in offering a much reduced bite angle for chelation (90IC1767), and electronically, due to the π-excessive nature of the imidazole ring compared to the π-deficient pyridine. Furthermore, double deprotonation of **62** leads to a dianion that acts as a doubly chelating binucleating ligand [90CCR(106)227]. Numerous mononuclear and binuclear complexes of this ligand have been reported, along with many X-ray structure determinations, as has been reviewed elsewhere [90CCR(106)227]. Similar complexes have been prepared from the electron-rich 4,4′,5,5′-tetramethyl derivative (75KK1054; 83IC3911) and the electron-deficient tetracyano analogue [84IC338, 84ICA(81)L15, 84ICA(86)107].

The 5′-amino derivative of **63** has been the subject of several studies in which it was cyclized to ethenoadenosines [70JCS(C)2206; 73TL3087; 75JOC1066; 76CPB1561; 80JA770].

F. Bioxazoles

There are six possible bioxazoles (**65–70**), of which only two are known. Surprisingly, the 2,2′-isomer (**65**) has not been reported, despite the fact that it ought to be accessible by coupling reactions, by direct synthesis from



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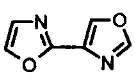

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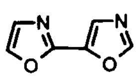

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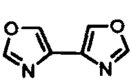

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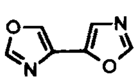

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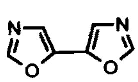
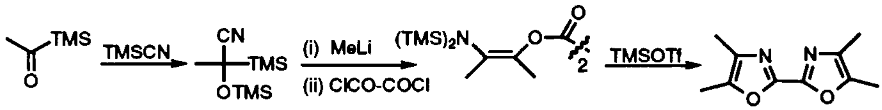


(70)

acyclic precursors, or by oxidation (94T2297) of the readily available 4,4′,5,5′-tetrahydro derivative (2,2′-bioxazoline) [38JA2152; 81JCS(D)1492]. Such tetrahydro forms are readily available from aminoalcohols, and chiral derivatives have been much used as ligands for asymmetric catalysis (91AGE542; 94T2297). The tetramethyl derivative of **65** has been prepared using a new oxazole ring synthesis, as shown in Scheme 25 (92JOC3331). The 5,5′-diphenyl derivative has been prepared from 5-phenyloxazole by lithiation and treatment with tosyl fluoride (75LA533); much earlier, it was prepared from reaction of α-aminoacetophenone with oxalyl chloride and subsequent acid-catalyzed cyclization (55JA1850). Many tetraaryl deriv-

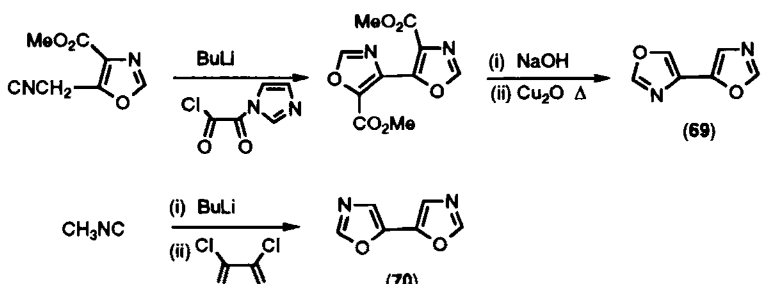


SCHEME 25

atives have been made by similar cyclizations (70CB1572). The tetraphenyl derivative has also been isolated as the product of photolysis of 4,5-diphenyloxazole; its X-ray structure was determined [92PIA(A)569], as was that of another 5,5′-diaryl derivative (93MI7).

Although the parent 2,4′-isomer (**66**) has not been reported, derivatives have been much studied of late because of the isolation (86JA846; 91JA2303, 91JA3173) of several marine natural products (e.g., hennoxazole A, Fig. 1), which contain bioxazole and teroxazole subunits with 2,4′-linkages. It has been suggested that such compounds might be biosynthesized from polyketides by a mechanism involving naturally occurring Beckmann rearrangements (86JOC5300); however, serinylserine would seem to be a much more logical biosynthetic precursor. In the course of studies toward the total syntheses of such compounds (92JHC607; 93AGE1), several methods have been developed for the preparation of substituted 2,4′-bioxazoles. These include iterative cyclizations (90SL36; 93JOC5759), repetitive rhodium-catalyzed cycloadditions of nitriles with diazo compounds (92TL2159, 92TL7769; 94T3761), and the double cyclization of a dipeptide derivative (93JOC3604). Other substituted derivatives of **66** have been prepared as prostacyclin mimetics (93JMC3884).

The 2,5′-isomer (**67**) has not been reported, but the 2′-phenyl and 2′-heteroaryl derivatives have been synthesized by multistep procedures (86KGS826). Neither the parent 4,4′ isomer (**68**) nor simple substituted derivatives have been reported. However, both the 4,5′ and 5,5′ isomers, **69** and **70**, have been synthesized via the Schollkopf procedure that involves the acylation of α-metallated isocyanides. Thus, as shown in Scheme 26,



(69)

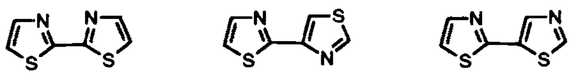
(70)

SCHEME 26

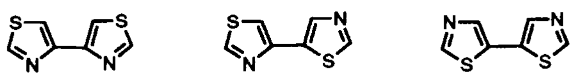
69 was prepared from a preformed oxazole precursor, whereas **70** was prepared directly from methyl isocyanide and oxalyl chloride (79LA1370). Both compounds were fully characterized spectroscopically. Since this is the only report of the synthesis of unsubstituted bioxazoles, the structures and chemistry of these compounds are totally unexplored.

G. Bithiazoles

a. *Synthesis.* For a number of reasons these are a particularly well-studied group of compounds. All six isomers (**71**–**76**) were prepared about 50 years ago by Swiss chemists, generally using the standard (Hantzsch)



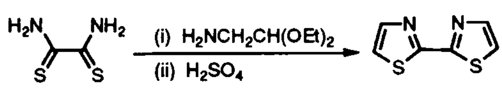
(**71**) (**72**) (**73**)



(**74**) (**75**) (**76**)

method of thiazole ring formation, by reaction of a thioamide with an α-halocarbonyl compound. The six isomers have more recently been prepared by palladium-catalyzed (Stille) cross-coupling of bromothiazoles with trimethylstannylthiazoles (87S185).

The 2,2′-isomer (**71**) was first prepared by Ullmann homo-coupling of 2-bromothiazole (39HCA698), a reaction that is better performed using nickel as the coupling catalyst (88AJC1625; 94T11893). It has since been prepared, in high yield, by coupling of thiazole with 2-trimethylsilylthiazole via an *N*-ethoxycarbonyl salt (84TL3637) and by the palladium-catalyzed cross-coupling procedure (87S185). It can also be prepared (Scheme 27) by a double cyclization reaction from dithiooxamide (rubeanic acid) (88BSB731). Many symmetrically substituted derivatives have been prepared by similar reactions of dithiooxamide with haloketones (44HCA489, 44HCA624; 47HCA1160; 68JIC1056). 2-Chlorooxiranes have been used

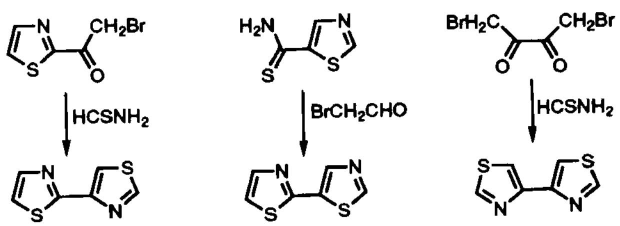


(**71**)

Scheme 27

as masked α-haloaldehydes for this purpose (81T2607). Other preparations of substituted derivatives of **71** include oxidations of bithiazolines [57LA(610)49]; Gabriel-type syntheses (59JOC1861); the reaction of dithiooxamide with oxalbisphenylimidoyl chloride (88JHC901); and reactions of α-mercaptoketones with liquid HCN (75LA410). Unsymmetrically substituted derivatives of **71** have been prepared by procedures involving sequential ring constructions [52HCA187; 77JMC946; 92IJC(B)782]. A highly fluorescent tetrasubstituted derivative (vitachrome) is a product of oxidation of thiamine (vitamin B_1) (43HCA1778), whereas the 4,4′-dicarboxylic acid derivative of **71** is a product of the alkaline decomposition of cystine (63CB438). Substituted derivatives of **71** have also been incorporated into macrocycles [92JCS(P1)383], cryptates (89TL2209; 92HCA1221; 93IC572) and polymers [65JPS(A)3117; 87MI1; 88SM(26)259; 93MM4450; 94CM1526].

The 2,4′-isomer (**72**) was first prepared by the Hantzsch reaction of thioformamide with 2-bromoacetylthiazole (Scheme 28), but this precursor is not readily available (48HCA1142). It has also been prepared by the Stille procedure (87S185) and by zinc reduction of the 2-chloro derivative, which is a by-product of the diazotization of 2-aminothiazole [95AX(C)72]. The Hantzsch procedure has been employed to prepare many substituted derivatives of **72**, often for biological screening [60JCS909; 66NKZ594; 67CB2188; 77IJC(B)727; 86G133; 92JIC231; 93JIC607]. However, by far the most common reason for synthesizing derivatives of **72** is in relation to naturally occurring compounds that contain this component. Most notable among these are the bleomycins, important antibacterial and antitumor agents that are used for clinical treatment of certain cancers. The correct structure for bleomycin was first proposed in 1978 (78JAN801), and total syntheses of bleomycin A_2 soon followed (82JA5537, 82TL521; 94JA5619). The bithiazole-containing fragment of bleomycin had been synthesized much earlier (70JHC1439). In many other studies, 4,2′-disubstituted derivatives of **72** have been synthesized as analogues to probe the mode of action



(72) (73) (74)

SCHEME 28

of bleomycin (81JHC1213; 82B3711; 84JHC681; 85NAR6703; 92BMCL261, 92SL59; 94JBC10899; 95JA9107).

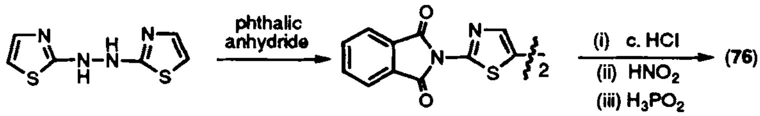
Many other important natural products, mostly antibiotics, that contain **72** as a subunit have been isolated, characterized, and in some cases synthesized. These include myxothiazole (see Fig. 1) (80JAN1474, 80JAN1480; 93NPR565, 93TL5151), cyclothiazomycin (91JAN582, 91TL221; 95CL45), the micrococcins [66JCS(C)1354, 66JCS(C)1371; 91TL4263], the tallysomycins (77JAN789), and saramycetic acid I (67AAC456; 91TL217). In the syntheses of such compounds the bithiazole unit has generally been constructed by either Hantzsch reactions or transition-metal-mediated coupling reactions, whereas in the natural products the biosynthetic origin is from cysteinylcysteine (77JA8078). Several other interesting natural products contain a reduced form of **72** as a thiazole–thiazoline subunit, with as many as four contiguous thiazol(in)e rings. These include the phleomycins (93JA12605), tantazoles (90JA8195), mirabazoles (91TL2593; 94SL587), and thiangazole, an HIV-1 inhibitor (94JOC4733, 94SL702, 94TL5707; 95JOC7224).

The 2,5′-isomer (**73**) has been prepared by a Hantzsch synthesis (Scheme 28), by decarboxylation of the 5-carboxylic acid (50HCA1960), and by the Stille method (87S185). The 2-chloro derivative is also a minor byproduct in the diazotization of 2-aminothiazole [95AX(C)72], whereas trisubstituted derivatives have been reported to be formed, in high yield, from reactions of α-haloketones with *N,N′*-dimethyl-2,4-dithiobiuret (77CL1299).

The symmetrical 4,4′-isomer (**74**) is readily prepared by a Hantzsch synthesis (Scheme 28) (39HCA938). It has also been made by reaction of the 2,2′-dihydrazino derivative with mercuric oxide (56CB2777) and by cross-coupling (87S185). The 2,2′-diphenyl derivative has been reported to form, in modest yield, from the reaction of benzonitrile with thioglycolic acid (81JHC877), whereas other symmetrically substituted derivatives have been prepared by Hantzsch syntheses [48HCA2065; 62YZ257; 77IJC(B)727; 94TL4401].

The 4,5′-isomer (**75**) has been prepared by the Hantzsch method, although the precursor chloroketone is not easily accessible (48HCA26), and by a cross-coupling reaction (87S185). Various substituted derivatives have been prepared by Hantzsch methods [40CB28, 40JPJ127; 62ZOB984; 74LA1195; 76IJC(B)552; 80AJC2291; 85AJC1257].

The unsubstituted 5,5′-isomer (**76**) is not readily available by the Hantzsch method. It was first prepared (Scheme 29) by diazotization of a diamino derivative (53HCA354) obtained by a benzidine-like rearrangement (51CB518), and has since been prepared by cross-coupling of the chloro- and trimethylstannyl-thiazoles (87S185). The 4,4′-bis(ethoxycarbonyl) derivative has been prepared from thiooxalic esters by reaction



SCHEME 29

with ethyl isocyanoacetate (83SUL199). Substituted derivatives of **76** have been prepared by Hantzsch syntheses using 2,3-dibromo-1,4-diketones (48HCA2065).

b. *Physical Studies.* X-ray crystal structures have been determined for five of the six isomers. The solid-state structures of **71** (88AJC1625), **73** [95AX(C)76], **74** (88AJC1625), and **76** [95AX(C)76] all show planar, or near planar, transoid conformations, whereas that of **72** [95AX(C)72] is centrosymmetric, which requires a planar disordered structure. X-ray structures have also been reported for the 4,4′-dimethyl [87AX(C)1171] and 4,4′-diacetoxy-5,5′-dimethyl [71AX(B)1817] derivatives of **71.** In connection with the structure elucidation of natural products, X-ray structures of several derivatives of **72** have been determined, such as a derivative of the antibiotic micrococcin P [66JCS(C)1361], an acid hydrolysis product of bleomycin A_2 (68TL4635), and a degradation product of myxothiazole (81TL3829).

Relatively little spectroscopic work has been reported for the unsubstituted bithiazoles. The ^{1}H and ^{13}C NMR spectra of **71** have been assigned (88BSB731, 88IC1025). In a recent UV study of five of the isomers (**75** was not considered), theoretical calculations were used to study the conformations and barriers to rotation of these compounds (93SPL1889). Molecular orbital calculations were also used to rationalize the observation that substituted derivatives of **72** undergo photoisomerization to the corresponding derivatives of **71** and **74** (86TL6389; 88TL3963), reactions that also occur for bleomycin (86JA7089; 87JA938).

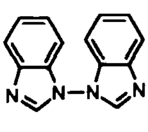
c. *Reactions.* The 2,2′-isomer (**71**) has been dimethylated and *N,N′*-bridged to dithiazolium salts (90TL1539), the former undergoing reaction with potassium superoxide to 10-membered ring products (92TL6983; 93T4859). Halogenation reactions have been carried out on derivatives of **72** (93JA12171). The 2,2′-diamino derivative of **74** is nitrated in the 5,5′ positions (84JIC151), whereas the corresponding dianilino compound undergoes cyclocondensation with malonate derivatives to mesoionic bispurinone analogues (88JHC571). Various transition metal complexes have been reported by the two chelating ligands **71** [40HCA1268; 41HCA869;

87HCA2073; 88AJC1625, 88BSB731; 92JOM(441)143] and **74** (40HCA-1268; 41HCA869; 82IC1714; 85AJC851), which have particularly low-energy π^* orbitals. A very detailed ^1H and ^{13}C NMR study of the ruthenium complexes of **71** has been reported (88IC1025).

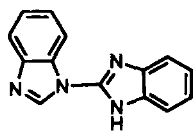
H. Benzo Derivatives

1. *Bibenzimidazoles*

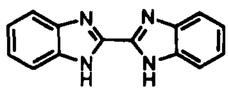
a. *Synthesis.* There are three possible bibenzimidazoles (**77**–**79**) that are linked through the five-membered rings. The N–N linked 1,1′-isomer (**77**) has not been isolated, although it has been claimed that a crystalline



(**77**)



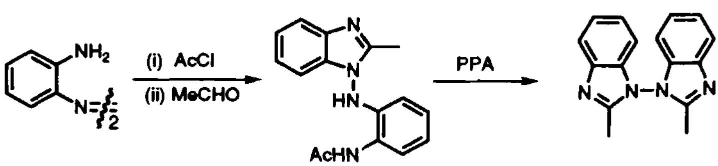
(**78**)



(**79**)

nitrate salt of protonated **77** is formed from reaction of benzimidazole with organotin nitrates [80ICA(40)183]. The 2,2′-dimethyl derivative has been prepared from *o,o*′-azoaniline by two successive cyclizations, as shown in Scheme 30 [81JCS(P1)403]. The 2,2′-diphenyl derivative has been obtained by treatment of *N*-benzylidene-*o*-phenylenediamine with cuprous chloride in pyridine and oxygen (81ACH37), and this has been extended to the preparation of other 2,2′-diaryl derivatives (86JOC218).

The 1,2′-isomer (**78**) has only been prepared, in low yield, by thermolysis of 2-phenylthiobenzimidazole (75BCJ956). The 1′-methyl and 2,1′-dimethyl derivatives of **78** have been reported from reactions of the appropriate benzimidazole with 1-methylbenzimidazole-2-sulfonic acid (75KGS826) and 2-chloro-1-methylbenzimidazole (67MI1). The 2-oxo derivative of **78** has been prepared from 2-chlorobenzimidazole (82AJC775), and the 2-

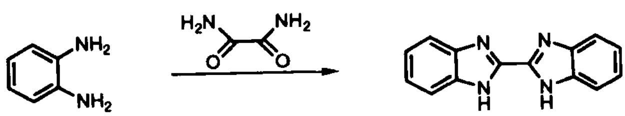


Scheme 30

thione derivative from benzimidazole-2-thione (85PJC921). The product of the latter reaction has been cyclized to a pentacyclic compound by reaction with thiophosgene [84JPR(326)159].

The 2,2′-isomer (**79**) is a very well-studied compound that has been known for more than a century [1881LA(209)370]. It is generally prepared by reaction of *o*-phenylenediamine with oxamide (Scheme 31) [53JCS2238; 55JCS1079; 58LA(616)87; 78IC2078] or with trichloroacetic acid [67JCS(C)20; 70ZN(B)945]. The former reaction has, however, been shown to produce about 20% of an isomeric compound, fluoroflavin [72LA(765)110]. Reaction of *o*-phenylenediamine with other oxalic acid derivatives, such as oxamidines (58JOC262) and imidates (64CB1599), also gives **79.** However, oxalic acid itself does not normally produce **79** [58JOC262, 58LA(616)87], unless in the presence of polyphosphoric acid (80CIL287), when the reaction proceeds in high yield. In contrast to the reactions of benzoxazole and benzothiazole (see later discussion), photolysis of benzimidazole does not produce the 2,2′ isomer (**79**), but rather a mixture of 2,4′ and 2,5′ isomers (73TL2987). It is, however, formed from the photolysis of 2-(2′-furyl)benzimidazole (fuberidazole) [92ZN(B)1431] and has been prepared by metal-catalyzed coupling of benzimidazole (89CPB1987) and from 2-methylbenzimidazole by the Willgerodt–Kindler reaction (91MI5). The 1,1′-dimethyl derivative of **79** has also been prepared by coupling of 1-methylbenzimidazole with various metallating reagents (58JOC1791; 67KGS955; 68T4445; 79KGS200) and with dichlorocarbene [87H(26)1161].

b. *Physical Studies.* Analysis of the spectra of the 2,2′-dimethyl derivative of **77** suggested twisting about the N—N bond [81JCS(P1)403]; this was confirmed, for a diaryl derivative, by an X-ray structure determination that showed an angle of 71.9° between the planes of the two benzimidazole rings (86JOC218). Theoretical studies and physical measurements have been reported for **78** and its derivatives (70KGS328, 70KGS515). The X-ray crystal structure of **79** has been determined (88MI3) and theoretical calculations reported [71MI2; 94IJC(A)651]. Various physical and



(79)

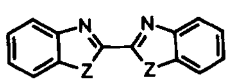
SCHEME 31

spectroscopic properties of **79** have also been described (80KGS1662; 89CJC1200, 89MI2).

c. *Reactions.* The 2,2′-isomer (**79**) is readily alkylated to 1,1′-disubstituted derivatives, including 1,1′-bridged compounds [70ZN(B)931], and has been converted to 1,1′,3,3′ doubly bridged bibenzimidazolium salts (95CB131), which have recently been converted to ureaphanes by oxidative cleavage of the central C—C bond (94TL33; 95JOC5935). Oxidation of **79** leads to the $\Delta^{2,2'}$-dehydro derivative (63JOC1931), whereas reaction with boron trifluoride produces a highly fluorescent, 1,1′-BF_2-bridged species (93HAC609). As with 2,2′-biimidazole, by far the most common use of **79** has been as a chelating ligand in coordination chemistry. Complexes of **79** with various transition metals, far too numerous to list here, have been reported and several X-ray structures determined. Furthermore, the doubly deprotonated form of **79** can, like its imidazole analogue, act as a binucleating ligand that bridges two metal centers separated by about 5.5Å. This is similar to the binuclear complexes of 2,2′-bipyrimidine (see later discussion), but, because of the dianionic nature of the ligand, has the advantage of reducing the repulsion between the positively charged metal centers (87IC4148). This area has been previously reviewed [89CCR(93)205; 90CCR(106)227].

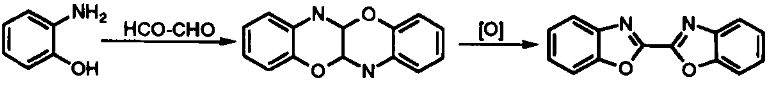
2. *Bibenzoxazole, Bibenzothiazole*

These two compounds are readily available by condensation of *o*-amino (thio)phenol with oxalic acid derivatives. 2,2′-Bibenzoxazole (**80**) was first prepared more than 70 years ago, but was incorrectly formulated as a benzoxazinobenzoxazine (25HCA16). It is readily prepared by oxidation,



(80) Z = O
(81) Z = S

using permanganate (59BCJ827), manganese dioxide [72LA(765)110], or photolysis (86CB3316), of the condensation product from *o*-aminophenol and glyoxal. However, as shown in Scheme 32, this compound is not the previously supposed bibenzoxazoline [59BCJ827; 72LA(765)110], but a tetrahydrobenzoxazinobenzoxazine, as proved by an X-ray crystal structure



(80)

SCHEME 32

determination (86CB3316); nevertheless, oxidation leads to **80.** It has also been prepared by reaction of *o*-aminophenol with less readily available oxalic acid derivatives, such as imidates (64CB1599) and thiono esters (75AP526), and by ring closure of just one of the oxazole rings [77H(6)941; 78H(10)57; 82BCJ873]. It can be synthesized by dimerization of benzoxazole either by reaction with dichlorocarbene [87H(26)1161] or, in high yield, by photolysis (74TL375); in fact, photolysis of benzisoxazole or saliconitrile also produces **80** (74TL375). 2,2′-Bibenzoxazole (**80**) and various derivatives substituted in the benzo ring have recently been reported, along with their infrared spectra (91MI4). The fluorescence and redox properties of **80** have also been studied (72JA2414; 82MI1). Reaction of **80** with lithium aluminium hydride results in ring opening to an ethylene diamine derivative [72LA(765)110].

2,2′-Bibenzothiazole (**81**) is even better-studied, having been known for more than a century (1880CB1223). It is readily prepared from reaction of *o*-aminothiophenol with oxalyl chloride (26JA248; 33M186; 68MI2), diethyl oxalate [1880CB1223; 56LA(599)44; 58JOC1344], cyanogen (1887CB2251; 58JOC262), oxalic acid (61JOC3434), oxamidines (58JOC262), oximidates (64CB1599), oxalthiono esters (75AP526), and even 1-nitro-2,2-bis(methylthio)ethylene (76ZC272). It has also been reported to result from Raney nickel reduction of 2-mercaptobenzothiazole (57JCS1652) and photolysis of 2-chlorobenzothiazole [87ZN(B)1153]. 2,2′-Bibenzothiazole can be prepared from benzothiazole itself by photolysis (74TL375) and by reaction with lithium metal (73SC135) or dichlorocarbene [87H(26)1161]. It also results from treatment of tris(2-benzothiazolyl)phosphine with aryl lithiums [90H(30)347; 93HAC421] or, more directly, by reaction of 2-benzothiazolyl lithium with phosphorus halides (94HAC409).

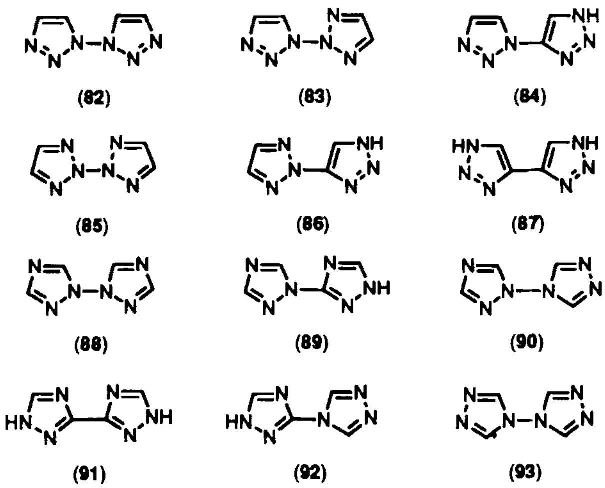
Several spectroscopic (71CJC956; 78MI2; 93SPL1771) and electrochemical (82MI1) studies have been reported on **81.** Like its oxygen analogue, **81** undergoes reductive ring opening on reaction with lithium aluminium hydride [72LA(765)110]. *N,N′*-Dimethylation produces bibenzothiazolium salts, which can be reduced to $\Delta^{2,2'}$-derivatives [72LA(765)110] and undergo reaction with potassium superoxide to give 10-membered ring products (92TL6983). Despite the intense current interest in the coordination chemistry of 2,2′-bibenzimidazole and 2,2′-bithiazole, no coordination chemistry of **81** has yet been reported (95UP1).

IV. Five-Membered Rings: Three or More Heteroatoms

A. Bitriazoles

1. *Bi-1,2,3-triazoles*

These are not well studied. Of the six possible isomers, **82–87**, only the C–C linked isomer, 4,4′-bi-1,2,3,-triazole (**87**), is known. It was prepared as outlined in Scheme 33 and fully characterized by spectral methods (89CB1175). Substituted derivatives have been known for some time

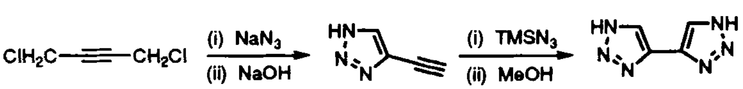


(**82**) (**83**) (**84**) (**85**) (**86**) (**87**) (**88**) (**89**) (**90**) (**91**) (**92**) (**93**)

(58CB1841). The two symmetrical N–N linked isomers, **82** and **85**, have been the subject of MNDO calculations (84CJC687).

2. *Bi-1,2,4-triazoles*

a. *Synthesis.* These are considerably better studied than their 1,2,3-isomers. Disregarding individual tautomers, there are six possible isomers,



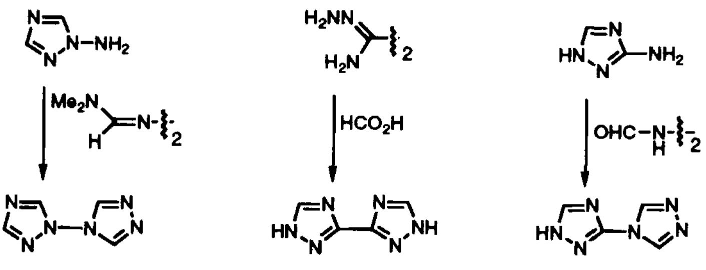
(**87**)

SCHEME 33

88–93, of this class. The only literature reference to the 1,1′ isomer (**88**) is a recent, but obscure, mention of its anticorrosive properties (92JCPB2011). Although the 1,3′ isomer (**89**) has apparently been alkylated with propargyl bromide (82MI2), its synthesis has not been reported. The 3,5-dimethyl derivative of **89** was prepared, in low yield, by reaction of 3-hydrazino-1,2,4-triazole with diacetamide (54JCS4508). Other methyl derivatives were prepared, in better yields, by nucleophilic substitutions of halotriazoles with sodium triazolate (77JHC397). Other substituted derivatives have been prepared by triazolate displacement of nitro groups in dinitrotriazoles (80KGS257, 80KG1553; 93ZOR2304). The 1,4′ isomer (**90**) has been prepared (Scheme 34) by reaction of 1-amino-1,2,4-triazole with dimethylformamide azine [80JCR(S)50].

The C–C linked isomer (**91**) has been known for almost a century. It was first prepared (Scheme 34) by reaction of oxalamidrazone with formic acid (1897CB1193) and has since been prepared using formaldehyde (36MI1). This method was also used to prepare various substituted derivatives. Other substituted derivatives have been prepared by a variety of synthetic approaches. 5,5′-Disubstituted derivatives have been made by reactions of imidic esters with oxalamidrazone (63CB1064) and oxal-bis-hydrazide (74ZOB115), and by reactions of oxalimidic esters with arylamidrazones [68LA(714)122]. Trisubstituted derivatives have been prepared by reactions of imidic esters and triazolecarboxhydrazides (62JCS5149). 4,4′, 5,5′-Tetraaryl derivatives have been made from the combinations of diaryloxalimidyl chlorides with benzhydrazide (58JA5786), oxalyl chloride with arylbenzamidrazones (68CB4238), and, most recently, from oxalodihydrazonyl diazides via either diamidrazones or bis-phosphinimines (93T2761).

The 3,4′ isomer (**92**) is readily prepared (Scheme 34) by reaction of 3-amino-1,2,4-triazole with *N*,*N*′-diformylhydrazine (53JOC1368). The 4,4′-



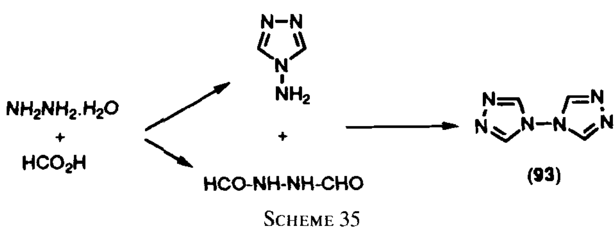
(**90**) (**91**) (**92**)

SCHEME 34

isomer (**93**) has also been prepared by several different methods. It was first made by reaction of 4-amino-1,2,4-triazole with dimethylformamide azine [67JCS(C)1664] and, subsequently, with the more readily available diformylhydrazine [79ZN(B)1500]. It is also produced by reaction of dimethylformamide azine with hydrazine [80JCR(S)50]. However, the most convenient procedure (Scheme 35) uses only hydrazine hydrate and formic acid and involves the generation, by stoichiometric control, of separate solutions of 4-amino-1,2,4-triazole and diformylhydrazine, which are then mixed and heated to produce **93** [79ZN(B)1500]. Methyl-substituted derivatives of **93** have been prepared, from tricyclic precursors, by oxidation and decarboxylation (73KGS285), and by Raney nickel desulfurization (77JHC397).

b. *Physical Studies.* The conformations of all three N–N linked isomers have been the subject of MNDO calculations (84CJC687). The X-ray crystal structures of **92** [91AX(C)1866], **93** (77CSC503), its 3-chloro-5-nitro derivative (82ZSK171), and the 5,5′-dinitro derivative of **91** (82K485) have all been reported. In the solid state, **92** exists as the (1H)-3,4′ tautomer with a dihedral angle of only 8.5° between the two rings; the bonding geometry and ultraviolet spectrum were interpreted to show partial conjugation between the rings. In contrast, the two rings of **93** are orthogonal (91.9°) and at an angle of 74° in the 3-methyl-3′-phenyl derivative (77ZSK1095). Crystal structures of several metal complexes of **93** have also been reported [87AX(C)1527; 90POL2971; 91JC3167; 94G509). ^{1}H and ^{13}C NMR, UV, IR, and mass spectra of many of the preceding compounds have been assigned.

c. *Reactions.* Very little reaction chemistry has been reported for these compounds. The 5,5′-diamino derivative of **91** has been converted to the dinitro derivative (70KGS259) and to nitroamine salts by reaction with tetranitromethane (87ZOR2236), and its coordination chemistry has been investigated [94ICA(227)181]. Mono- and dinuclear molybdenum carbonyl complexes of **91** have been reported [76ZAAC(432)97]. An interesting pH

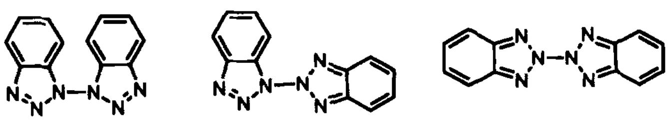


SCHEME 35

dependence of the physiochemical properties of ruthenium complexes of the 5,5′-dimethyl derivative of **91** has been described [90ICA(171)223]. The 4,4′-isomer (**93**) is readily quaternized to the 1,1′-dimethyl dication [85JCS(P1)1209] but, unlike other triazoles, fails to react with tetracyano-ethylene (82JOC4409).

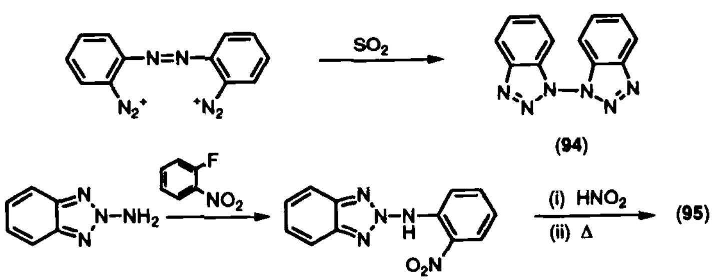
3. *Bibenzotriazoles*

Two of the three possible isomers (**94–96**) are known. The 1,1′-isomer (**94**) was prepared (Scheme 36) by treatment of *o,o*′-azobenzene bis-diazonium salt with sulfur dioxide (67JA2643). Recent attempts to pre-



(**94**) (**95**) (**96**)

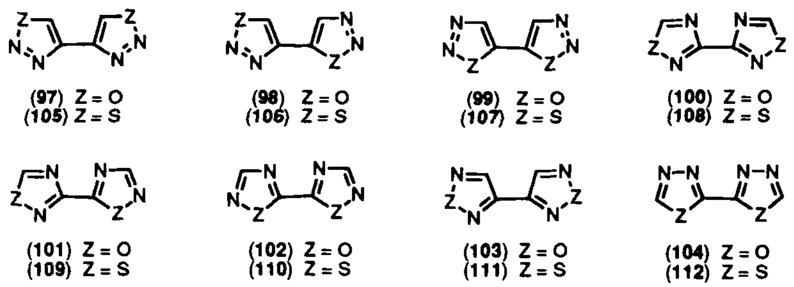
pare **94** by other methods were unsuccessful [95H(41)131]. The 1,2′-isomer (**95**) has been prepared from 2-aminobenzotriazole in a three-step sequence involving construction of the second benzotriazole ring (Scheme 36) (67JA2643). Both **94** and **95** are reduced to benzotriazole by treatment with aluminium amalgam and lithium aluminium hydride, respectively, and both undergo thermolysis, with loss of dinitrogen, to give interesting tetracyclic dibenzotetraazapentalenes (67JA2643). Attempted lithiation of **94** resulted in cleavage of the inter-ring bond [95H(41)131]. The 2,2′-isomer (**96**) is not known.



SCHEME 36

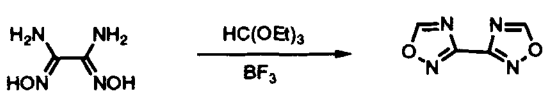
B. Bioxadiazoles

a. *Synthesis.* There are eight isomeric bioxadiazoles (**97**–**104**). None of the three bi-1,2,3-oxadiazoles (**97**–**99**), or any simple substituted derivative, is known. 3,3′-Bi-1,2,4-oxadiazole (**100**) has been prepared by a dou-



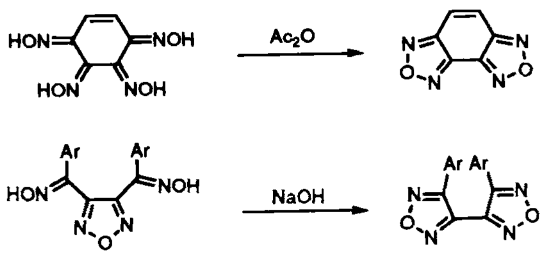
ble cyclization reaction, as shown in Scheme 37 (62HCA441; 94KGS539). Several 5,5′-disubstituted derivatives have been prepared by similar reactions between oxalamidoxime and other carboxylic acid derivatives (1889CB2946; 63BSB91; 66HCA1430; 86S490). The 5-trifluoromethyl derivative of **100** has been made with sequential construction of the two rings [73JCS(P1)47]. The unsymmetrically linked 3,5′ isomer (**101**) is not known. Although the parent 5,5′ isomer (**102**) has not been reported, substituted derivatives have been made by several methods. Reactions of alkylamidoximes with oxalic acid derivatives give 3,3′-dialkyl derivatives (65JOC3734; 67BSB92), whereas 3,3′-diaryl derivatives have been prepared by dipolar cycloaddition of aryl nitrile oxides to cyanogen (88HCA1681) and, much earlier, by sequential ring constructions (1889CB3130). An interesting quater-1,2,4-oxadiazole, which contains both 3,3′ and 5,5′ links, has also been prepared (63BSB91).

Although 3,3′-bi-1,2,5-oxadiazole (bifurazan) (**103**) itself has not been reported, substituted derivatives are well known. The earliest of these is the 4,4′-vinylene-bridged derivative, which was prepared (Scheme 38) by dehydration of a tetraoxime (1887CB1607). 4,4′-Diaryl derivatives were



(**100**)

Scheme 37

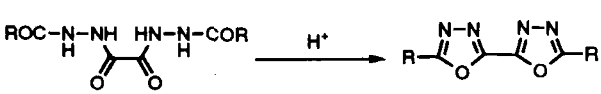


SCHEME 38

prepared (Scheme 38) by dehydration of monofurazan dioximes (33G159), whereas the simplest derivative, the 2-*N*-oxide (furazanylfurazone), was isolated from a reaction of α-isocyanilic acid (75LA1029). The 4,4′-diamino and dinitro derivatives were prepared some years ago (68JHC83) and have been converted into various other substituted derivatives [86S490; 88IZV2363; 92IZV1922; 93PS(78)309; 94MC138, 94OPP331; 95MC25]. The 4,4′-dicyanato derivative was prepared by thermolysis of benzotrifuroxan (91IZV1914), and the bifurazan subunit has been incorporated into macrocycles (94MC102).

2,2′-Bi-1,3,4-oxadiazoles are also readily available. Although the parent compound (**104**) has not been reported, 5,5′-disubstituted derivatives have been prepared by cyclization of diacyl oxalhydrazides (Scheme 39) (12CB3116; 32MI1; 60ZOB1644; 63CB1049; 65JHC441; 86MI1). These precursors are readily available either by acylation of oxalhydrazide or by reaction of hydrazides with oxalyl chloride. The 5,5′-diphenyl derivative has also been made by oxidation of the bis(benzoylhydrazones) of glyoxal and mesoxaldehyde [69JCS(C)1416] and by reactions of tetrazoles with acyl chlorides (60CB2106; 92ZOB1367). Unsymmetrically substituted derivatives have been prepared by iterative ring constructions [85JPR(327)109].

b. *Physical Studies.* Early molecular orbital calculations were reported for all three isomeric bi-1,2,4-oxadiazoles (**100–102**) (67TCA383; 68T485). Studies using various spectroscopic techniques have been reported of substituted derivatives of **100** and **102** (64HCA942) and of diaryl derivatives of



SCHEME 39

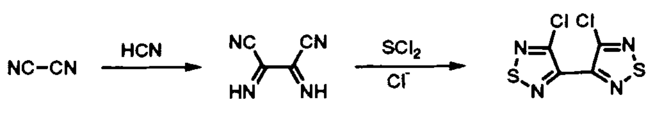
104 (60JOC872; 92MRC910). Multinuclear NMR studies have been reported for substituted derivatives of **103** (85MI1; 92KGS1101).

c. *Reactions.* Relatively little chemistry has been carried out on these compounds. The 5,5′-bis(trichloromethyl) derivative of **100** has been converted to other 5,5′-disubstituted derivatives (66HCA1430), whereas the 5,5′-bis(trifluoromethyl) analogue has been rearranged to a 3,4-diaminofurazan (88KGS856) and shown to form a σ adduct with sodium hydroxide (90KGS853). The 5,5′-bis(trifluoromethyl) derivative of **104** has recently been shown to undergo Diels–Alder reactions, although no bis adducts were produced (94PHA102).

C. Bithiadiazoles

None of the eight possible parent (unsubstituted) bithiadiazoles (**105**–**112**) is known. No bi-1,2,3-thiadiazoles have been reported. A disubstituted derivative of 3,3′-bi-1,2,4-thiadiazole (**108**) has been synthesized by sequential formation of each ring (92IZV174). Despite the extensive literature on their oxygen analogues (bifurazans), there have only been two recent reports on 4,4′-bi-1,2,5-thiadiazoles: the 4,4′-dicarboxy derivative of **111** was prepared by oxidation of a 4,4′-bridged (tricyclic) derivative (93CB2767), while the dichloro derivative was prepared from cyanogen by cyclization of diiminosuccinonitrile with sulfur dichloride, as shown in Scheme 40 (91CB1517). Bi-1,3,4-thiadiazoles are better studied, having been known for almost a century. Derivatives of **112** are readily prepared by cyclization of thioacyl derivatives of oxalhydrazide (57NKZ1588) or by treatment of acyl derivatives with P_4S_{10} [04JPR(70)423; 80JPR(322)933]. Amino derivatives are particularly well studied because of their ease of formation from thiocyanates (77BSB399; 91JIC365; 92MI6; 94T5091).

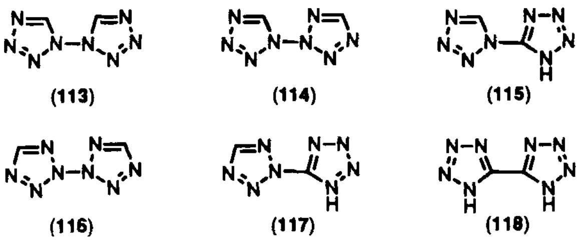
Very little chemistry has been carried out on these compounds. The dimethyl derivative of **112** has been shown to be a useful chelating ligand. A detailed study of a ruthenium(II) complex, including an X-ray structure determination, showed this ligand to be a strong π acceptor [91JCS(D)1043]. This ring system has been incorporated into macrocycles (94JOC3665).



SCHEME 40

D. BITETRAZOLES

a. *Synthesis.* There are six possible isomeric bitetrazoles (**113**–**118**). Although none of the three possible parent N–N linked bitetrazoles are known, the 5,5′-diphenyl derivative of 1,1′-bitetrazole (**113**) has been

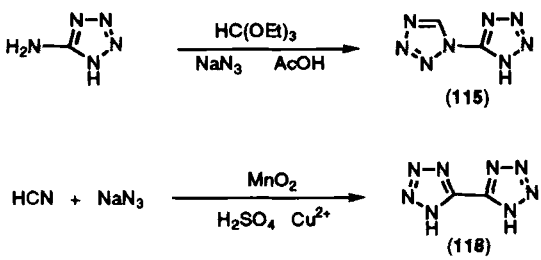


(113) (114) (115) (116) (117) (118)

synthesized and its thermolysis studied under a variety of conditions (62CB2546). 1,5′-Bitetrazole (**115**) has reportedly been prepared by heterocyclization of 5-aminotetrazole, as shown in Scheme 41 (85KGS1521). Substituted derivatives are also known (88ZOR2216). 5-Aryl derivatives of 2,5′-bitetrazole (**117**) have been reported (58JA3155).

Of the bitetrazoles, the 5,5′ isomer (**118**) is the best studied. It was first prepared in 1913, by reaction of hydrazoic acid with either cyanogen or 5-cyanotetrazole (13G465), and has since been prepared from oxalhydrazidine (36MI1) and from dinitroacetonitrile (64JOC2021). An improved method of preparation of **118** (Scheme 41) has since been described (86MRC984). Various aryl substituted derivatives of **118** have been prepared from *N*-arylnitrones (77JHC757) and from glyoxal hydrazones (87ZC407).

b. *Physical Studies.* An X-ray crystal structure of **118** showed a planar transoid structure, with the molecules forming chains held together by pairs of intermolecular hydrogen bonds [95JCX(ip)]. The pK_a and pK_b values



SCHEME 41

for **118** and its 1,1′-diphenyl derivative have been measured (81KGS1563) and these values used to determine the various Hammett constants for tetrazole substituents (83KGS1130). The heat of formation of **118** has been the subject of both experimental measurements (79JCED3) and theoretical calculations (93JEM205). ^{13}C and ^{15}N NMR studies of the parent compound and three mono- and dimethylated derivatives have been reported (86MRC984).

c. *Reactions.* 5,5′-Bitetrazole (**118**) reacts with benzoyl chloride to give a diacyl intermediate that spontaneously loses nitrogen and cyclizes to give 5,5′-diphenyl-bi-1,3,4-oxadiazole (92ZOB1367). The coordination chemistry of **118** has received some attention: an early study reported the preparation of several metal salts of **118** (20G256); a cobalt complex of **118** has been evaluated as a detonating agent (86MI2); a binuclear Au(I) complex of the dianion of **118** has been reported, in which the ligand acts in a monodentate mode with each metal (76IC1721); and ruthenium(II) and palladium(II) complexes of **118** and its 2,2′-di-*t*-butyl derivative have recently been reported, wherein the ligands act in a chelating coordination mode (95AJC1625).

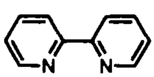
E. Other Systems

None of the many possible isomeric bioxatriazoles or bithiatriazoles is known. Not surprisingly, bipentazole is unknown.

V. Six-Membered Rings: One Nitrogen

A. Bipyridines

The chemistry of the six isomeric bipyridines (**119–124**) was covered in great detail in an excellent comprehensive review, published in this series



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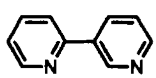

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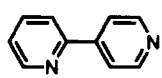

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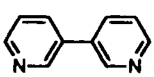

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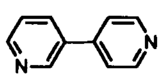

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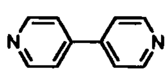


(124)

in 1984, which covered the literature up to the end of 1981 [84AHC(35)281]. Consequently, discussion of these compounds will be restricted to work published subsequently. However, the literature in this area is immense and a full coverage is beyond the scope of the present review; only selected, general aspects are covered, with references, where possible, to relevant reviews.

a. *Synthesis.* Of the six isomers, 2,2′-bipyridine (**119**) is by far the best studied because of its ability to form metal complexes with almost all metals in the periodic table, for which purpose it has been used for more than a century (1888CB1077) as the classical, bidentate, chelating heterocyclic ligand in analytical, organometallic, and coordination chemistry. Although it is, of course, commercially available, more than 50 new syntheses of **119** have been reported since the previous review, many of which are useful for the preparation of substituted derivatives. Indeed, many new procedures have been reported for the syntheses of all six isomers in the past 15 years. These most commonly involve either transition-metal-mediated homo-couplings of halopyridines, to give symmetrical bipyridines, or cross-couplings of halopyridines with pyridylorganometallics, which can be used to produce both symmetrical and unsymmetrical bipyridines (94KGS1536).

By far the most useful developments of the first type are the low-valent nickel-mediated coupling procedures [95AHC(62)305], which give much better yields than the classical Ullmann and Busch procedures. Numerous variations of this procedure exist, the most commonly used involving the *in situ* generation of a nickel(0) complex by zinc reduction of a nickel(II) precursor; this has been used to prepare all three symmetrical bipyridines (84S736). A useful variation, which results in considerably improved yields in certain cases, involves performing the reaction in the presence of tetraethylammonium iodide (90BCJ80). A more recent procedure employs liganded nickel complex reducing agents (94T11893) and this, too, was used to prepare the three symmetrical isomers.

The most commonly employed procedure of the second type is the palladium-catalyzed cross-coupling of halopyridines with trialkylstannylpyridines (the Stille reaction), which has been used to prepare five of the isomers, including all three asymmetrical isomers (86S564). More recent modifications to improve yields and shorten reaction times include the addition of silver oxide (92TL2199) or cupric oxide [93JOM(460)127]. All three unsymmetrical isomers have also been prepared by Suzuki cross-couplings of pyridylborates (84S936; 85CPB4755). A palladium-catalyzed cross-coupling of 2-bromopyridine with 3-pyridylzinc iodide was also used to prepare **120** (92TL5373). Bipyridines, and substituted derivatives, have also been prepared by reactions of Grignard reagents or organolithiums with various sulfur (84TL2549; 91HAC521, 91JOC6341) and phosphorus

[89TL567, 89TL6365; 90H(30)347, 90HAC295; 93HAC421; 94HAC409; 95TL4077] containing compounds.

A number of methods have been reported for the preparations of bipyridines that involve construction of a pyridine ring from acyclic precursors. The best-known of these is the Kronke procedure (76S1). A newer condensative-cyclization method is that developed by Potts, which uses a ketone and an α-oxoketene dithioacetal (85JOC5405; 93JA2793). A recently reported method for the preparation of monosubstituted derivatives of **119** involves the *in situ* generation, and subsequent reaction, of 2-pyridyl isocyanate [95TL327]. The well-established method of bipyridine synthesis by cobalt-catalyzed cotrimerization of acetylene with cyanopyridines (75S600) is likely to have more appeal in light of a recent photoinduced variation for preparing substituted pyridines under mild conditions [95JCS(CC)179]. Variations on most of these procedures have been used to prepare many substituted bipyridine derivatives, far too numerous to list here.

b. *Physical Studies.* Structural studies of bipyridines and their derivatives also represent an enormous amount of research effort. For example, a low-temperature X-ray structure of **119** has been reported (81JA4945), which shows a transoid planar structure in contrast to the cisoid structure of its monoprotonated salt (92IC1080). Reliable theoretical calculations of the structures and conformations of all six isomers have been reported (95JOC5291). Spectroscopic studies of bipyridines and their derivatives also abound in the literature. For example, complete assignments of the ^{13}C NMR spectra of all six isomers have been reported (92JOC6317).

c. *Reactions.* Chemical reaction studies of the various bipyridines are also too numerous to list. Again, the chemistry of the 2,2′-isomer (**119**) is the most studied because of its ability to complex metals. The homoleptic metal complexes of **119** have been the subject of review [89AIC(34)1]. Although this compound usually acts as a chelating ligand, examples are known of it bridging two metals [89ICA(157)151, 89POL2209; 91AJC219; 93IC3675]. Much of the chemistry carried out on the bipyridines has been for their incorporation as structural motifs in larger molecular and supramolecular species. Selected examples of such species include coordinating oligopyridines, helicates, catenates, rotaxanes, molecular knots, cryptands, podands, and molecular clefts; these have been the subject of several reviews (87CRV795; 90AGE1304; 91T6851; 92T10013; 93JA2793; 94PIC67; 95CRV2725).

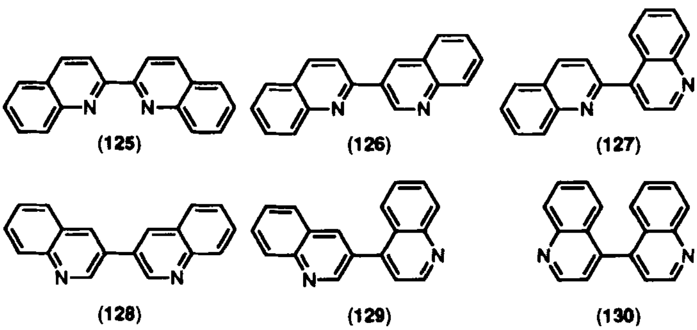
The 2,2′-bipyridine subunit has also recently been incorporated into numerous homochiral structures for use as chiral auxiliaries in asymmetric synthesis [e.g., 92CB453, 92TL3653, 92TL5165; 93JA5111, 93JCS(CC)1423,

93TA39, 93TA143, 93TL2661; 94AGE497, 94TL7973; 95JOC5386]. Of the naturally occurring bipyridines, the two that have attracted the most interest in recent years are a tetrahydroxy derivative of **119** (orelline) and its *N*-oxides, which are responsible for the toxicity of certain poisonous mushrooms (e.g., 93T8373), and the neurotoxic quaterpyridine nemertelline (Fig. 1), isolated from nemertine sea worms (95JOC7491). Synthetic bipyridines also show useful biological activities (e.g., 95BMCL2989).

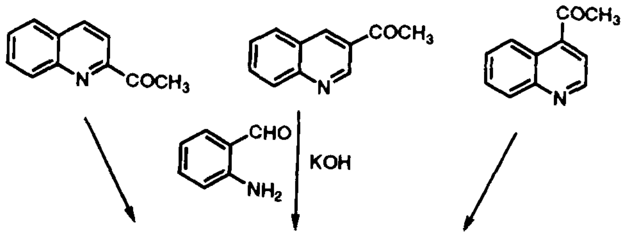
B. Benzo Derivatives

1. *Biquinolines*

a. *Synthesis.* There are six possible biquinolines (**125–130**) linked through the heterocyclic rings. 2,2′-Biquinoline (**125**) is the most studied. It is commercially available, under the name cuproine, having long been



used as an analytical reagent for copper (39MI1; 54AC1534). The first unambiguous syntheses of **125** were by the Friedlander method (21-HCA802), as shown in Scheme 42, and this procedure has been extended to substituted derivatives [53AC(R)242, 53JA4920], including 3,3′-bridged compounds (85JOC666). Low-valent nickel catalysts have recently been used for homo-couplings of 2-haloquinolines in several preparations of **125** [84S736; 86JOM(303)131, 86TL5483; 90BCJ80, 94T11893] and substituted derivatives (87OM2592; 90S279), which give better yields than earlier palladium-mediated (Busch) couplings (58JOC1375; 59YZ310, 59YZ314; 60YZ1510, 60YZ1515; 62YZ492, 62YZ498). 2,2′-Biquinoline (**125**) has also been prepared by oxidative coupling, often in low yield, of quinoline using various reagents [35RTC804; 56JCS616; 60JCS526, 60JOC372;



(125) (126) (127)

SCHEME 42

61LA(646)30; 63AJC1126; 68AJC207; 73YZ144; 74TL2373; 89JCR(S)388; 94EF990] and by coupling of quinoline *N*-oxide [66CPB557; 74IJC1238; 92H(34)2243]. It can also be prepared by thermal decarboxylation of the 4-carboxylic acid derivative (71KGS641) or the 4,4′-diacid (2,2′-bicinchonic acid, a commercially available analytical reagent) [67JPR(35)175]; by reaction of quinoline 2-sulfoxides with Grignard reagents (89BCJ2338); and by pyrolysis of quinolylgold compounds [80JOM(190)C56]. The 4,4′-dimethyl derivative of **125** has recently been prepared from *o*-(2-propenyl)aniline by double cyclization of an intermediate oxanilide (93S225) and by electrocatalytic oxidation of 4-methylquinoline (93CL257).

The 2,3′ isomer (**126**) has also been prepared by a variety of methods. Unambiguous syntheses include a Friedlander synthesis (Scheme 42) [1881M(2)491; 31M238]; decarboxylation of the 2′-carboxylic acid derivative (28JCS81); and palladium-catalyzed cross-coupling of halo- and dialkylboranyl-substituted quinolines [85H(23)2375]. It is also formed from reaction of quinoline with sodium metal (73ZOR2550; 89MRC4), sodium amide (20MI1), sodium hydride [92JCS(P1)759], selenium (40JPJ537), and rhodium on carbon (68AJC207). 2-Chloroquinoline has been reported to react with lithium to give **126** (75JA374), which is also formed, along with isomers and oligomers, from reaction of 1,2,3,4-tetrahydroquinoline with rhenium sulfide (91JA6574). Various substituted derivatives of **126** have also been prepared [61LA(644)93]. The 2,4′ isomer (**127**) has been synthesized only once, by the Friedlander method (Scheme 42) (60JOC1256).

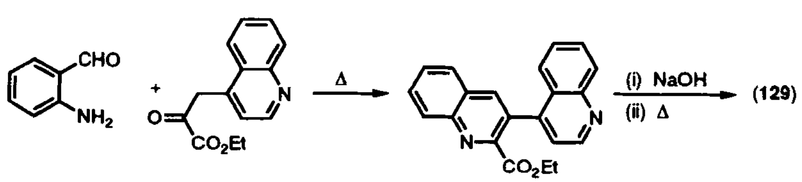
The symmetrical 3,3′ isomer (**128**) has most commonly been prepared by homo-couplings of 3-haloquinolines (31JPJ495; 85CPB4309), the best yields being obtained with nickel catalysts (86TL5483; 87AOC535; 94T11893). Various substituted derivatives have also been prepared by diverse synthetic routes (63IJC188; 68YZ453; 69CPB2178, 69CPB2389; 75CPB2949). The only preparation of 3,4′-biquinoline (**129**) has been by decarboxylation of the 2-carboxylic acid, obtained by a Friedlander synthe-

sis (Scheme 43) (28JCS81). A tribromo derivative of **129** has been made by reaction of 2,4-dibromoquinoline with potassium amide (73RTC304).

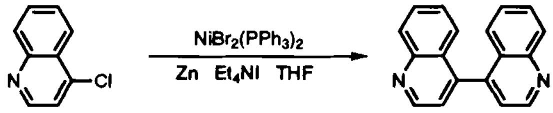
4,4′-Biquinoline (**130**) was first prepared from 1,2,3,4-tetrahydroquinoline by a multistep sequence (24JCS1608), but is best prepared (Scheme 44) by homo-coupling of 4-haloquinolines, preferably with nickel catalysts (84S736; 85CPB4309; 90BCJ80). It has also been prepared, in high yield, by desulfurization of di-4-quinolinyl sulfide (88JOC596). The 2,2′-dimethyl derivative of **130** has been prepared from 2-methylquinoline (quinaldine) via organosilicon intermediates (93JOC1926) and by electrocatalytic oxidation (93CL257). It and other symmetrically substituted derivatives have been prepared by homo-coupling reactions [78JCS(P1)1126; 86TL5483].

b. *Physical Studies.* X-ray crystal structures have been reported for **125** [77AX(B)3540] and **126** (91JA6574), both of which are planar in the solid state. Crystal structures have also been reported for many metal complexes of **125** [66INCL409; 76JCS(D)162; 77IC2334; 88JCS(D)2121; 94AX(C)394] and a trichlorodiiodate salt [79AX(B)1930]. The structure of the *N,N′*-dimethyl derivative of **130**, as an iodide salt, has also been determined [93AX(C)1398]. There have been several computational studies of the structure and electronic properties of **125** [68JCS(A)381; 72ZC304, 72ZC346; 80KGS1662; 85JCS(P2)811; 87IC4115; 94SA(A)2117]. Detailed NMR studies have been reported for **125** (82OMR42; 89MRC4), **126** (89MRC4; 91JA6574), and **128** [89JCR(S)388]. Various other physical measurements have been reported for **125**, including pK_a measurements (61JPC1196; 77KGS98), mass spectral studies (73KGS979; 76JHC981; 77SPL777), electrochemical studies [68JCS(A)381; 70JHC401; 86BSF733; 91JEC(313)243], ultraviolet spectroscopy (61JPC1196; 80LA291), Raman spectroscopy [82JCP(77)5288], and EPR studies (68SPL211; 86JPC1270; 90JPC8506). Infrared and ultraviolet spectra of **127** (60JOC1256) and **128** (80LA291) have also been reported.

c. *Reactions.* By far the most common use of **125** is as a chelating ligand in coordination chemistry. Compared to 2,2′-bipyridine (**119**), **125** is a much more sterically demanding ligand (67IC1102; 76IC3166; 93IC5779).



SCHEME 43



(130)

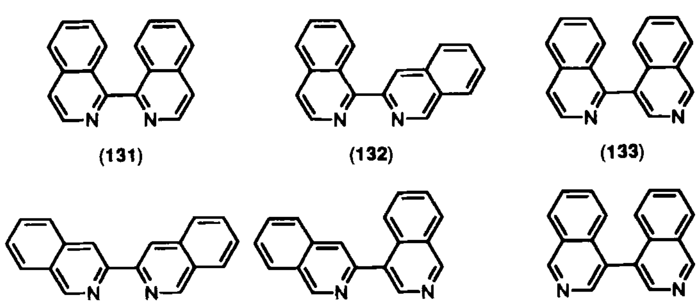
SCHEME 44

Its coordination chemistry up to 1989 has been reviewed [89CCR(93)205]. Since then many more transition metal complexes of **125** have been reported [89ICA(161)49, 89JCS(CC)516; 90HCA1306; 91OM1800, 91TMC(L)39; 92HCA1320; 93IC2341, 93ICA(207)121; 95ICA(228)81, 95POL1011], along with those of 3,3′-bridged derivatives [95T6941]. There have been several studies of the resolution and rates of racemization of the atropisomers of **130** [52JCS4133; 54CIL346; 71JCS(B)1907].

Relatively limited reaction chemistry of biquinolines has been reported. There have been several reports of oxidations of **125** and **126** to both mono- and di-*N*-oxides, and their subsequent conversion to various C-substituted derivatives (66JHC170; 75YZ1078; 76YZ1417; 81CPB3105; 85JOC666). The disulfonation of **125** has been reported [85JCS(D)2247], as has its reaction with trialkylaluminiums (83ZOB483) and conversion to diquinolo-imidazoles (90MRC1058).

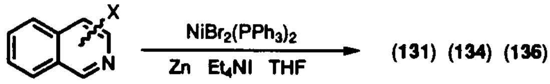
2. *Biisoquinolines*

a. *Synthesis.* Of the six possible biisoquinolines (**131–136**), only the three symmetrical isomers are known, each of which is best prepared by homo-coupling of the corresponding haloisoquinoline (Scheme 45). The



(131) (132) (133)

(134) (135) (136)



SCHEME 45

1,1′ isomer (**131**) was first prepared, in low yield, by Ullmann couplings of 1-bromoisoquinoline (52JOC471) and 1-chloroisoquinoline (57JOC514). The yields of these couplings are improved by the use of zero-valent nickel catalysts [87JCS(CC)1760; 90BCJ80]. It has also been isolated, usually in low yield, from various reactions of isoquinoline; these include reactions with rhodium on carbon (68AJC207), lithium diisopropylamide (74TL2373), and sodium naphthalenide [93IJC(B)889; 94T9079], and pyrolysis [77IJC(B)381; 77T3155] and aquathermolysis (94EF990). Reduction of isoquinoline by zinc in acetic acid gives a much-studied (72JOC3206; 77K182; 93CJC754) diacetyl-tetrahydro derivative that can be oxidized to **131** (57JOC514). It was also obtained as a by-product from a palladium-catalyzed cross-coupling of 1-iodoisoquinoline (85CPB4309). The 4,4′-dicyano derivative has been isolated from reaction of 4-cyanoisoquinoline with cyanide ions in dimethyl sulfoxide (74YZ1041).

The only literature reference to the 1,3′ isomer (**132**) is as a possible structure for a trace product formed, in negligible yield, from reaction of isoquinoline with rhodium on carbon (68AJC207). The 1,4′ isomer (**133**) has not been reported, the simplest known derivative being its 4-bromo-1′-cyano derivative (88CPB930). The 3,3′ isomer (**134**) was first prepared, in low yield by Ullmann coupling of 3-bromoisoquinoline (52JOC471), a reaction that would presumably be improved by nickel catalysis, as has been used in the more recent reports of preparations of the 1,1′-dimethyl (88HCA1042) and 4,4′-dihydroxy (90S279) derivatives of **134.** It has also been isolated as a by-product from a palladium-catalyzed cross-coupling of 3-trimethylstannylisoquinoline (82CPB2003) and, in negligible yield, from reaction of isoquinoline with Raney nickel (56JCS616).

The 3,4′ isomer (**135**) is not known. 4,4′-Biisoquinoline (**136**) was first prepared, in modest yield, by a Busch homo-coupling of 4-bromoisoquinoline (40JPJ536). Again, yields are greatly improved by nickel catalysis (90BCJ80; 94T11893). It has been made by a palladium-catalyzed cross-coupling of a 4-haloisoquinoline with 4-diethylborylisoquinoline [87H-(26)1603] and as a by-product from 4-trimethylstannylisoquinoline (82CPB2003). It was also formed as a by-product from reaction of 4-bromoisoquinoline with potassium amide (74RTC273) and, in modest yield, by oxidative workup of the product of an $S_{RN}1$ reaction of *o*-iodobenzylamine with acetone enolate (84T311). Substituted derivatives of **136** have been prepared by a variety of methods [77YZ1334; 85JCS(CC)885; 91JHC341].

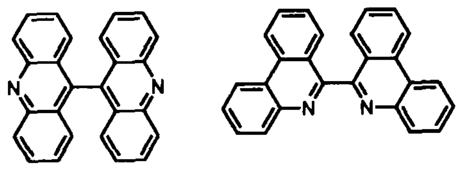
b. *Physical Studies.* There have been no X-ray crystal structure determinations of unsubstituted biisoquinolines. Recently, structures have been reported for the *N,N'*-dimethylated derivative of **131,** as an iodide salt [93AX(C)1398], and of ruthenium (94JA4801) and platinum (93POL1201) complexes of **131.** Structures of the 1,1'-dimethyl-*N,N'*-dioxide of **134** and its europium complex (90JCOC83), a ruthenium complex of **134** (92CL1887), and the 1,1',3,3'-tetrakis(dimethylamino) derivative of **136** [87AX(C)1142] have all been reported.

c. *Reactions.* Nitration of **131** occurs in the 5 (and 5') position(s) (72JOC3206), and the 3,3'-dimethyl derivative has been oxidized to the diformyl compound for incorporation into tetrapyrrole analogues, whose copper complexes have been investigated as cyclopropanation catalysts (94M325). *N,N'*-Diquaternized derivatives of **131** are chemiluminescent [67JCS(CC)476]. Much of the work with **131** has centered on its atropisomerism. Whereas **131** itself has long been known to undergo rapid racemization (54JCS3464), the *N,N'*-dioxide can be resolved into its enantiomers (92JHC931). In metal complexes of **131,** chelation requires a cisoid relationship of the two nitrogens, which results in a severe steric interaction between the 8 and 8' hydrogens; as a consequence, the coordinated ligand is nonplanar and chiral. Complete chiral recognition was observed in the complexation of **131** with homochiral cyclopalladated compounds [87JCS(CC)1760]. Several studies of ruthenium complexes of **131** have been reported (93IC3803, 93MI8; 94JA4801; 95JA2000), and the mechanism of interconversion of the atropisomers of the coordinated ligand has been investigated by NMR spectroscopy (94JA4801; 95JA2000). Rhodium complexes of the 7,7'-dimethoxy derivative of **131** have also been reported [87JCS(CC)807].

Unlike **131,** the 3,3' isomer (**134**) offers no steric resistance to metal coordination and has long been known to form complexes readily (56JCS616). More recently, its luminescent ruthenium complexes have been much studied [82CPL(89)101; 83CPL(102)537, 83G731; 84CPL(104)-100; 85IC202, 85JPC3680; 86IC1738; 87IC4115; 90CPL(172)5], along with molecular orbital calculations (87IC4115) and luminescence studies (90CPL(172)5) of **134** itself. Despite the benzo fusion, this ligand has a relatively high-energy LUMO, and its metal complexes have relatively unstable MLCT states (87IC4115). Both **134** and its *N,N'*-dioxide have been incorporated into larger molecular structures, such as cryptates [88HCA1042; 90HCA106; 91HCA572; 93PAC563; 95AX(C)2232], and complexes with lanthanide metals have been investigated (90HCA106; 92HCA1621). The 4,4' isomer (**136**) can readily be resolved into atropisomers (54JCS3464), the racemization of which has also been studied (54CIL346).

3. *Biacridine, Biphenanthridine*

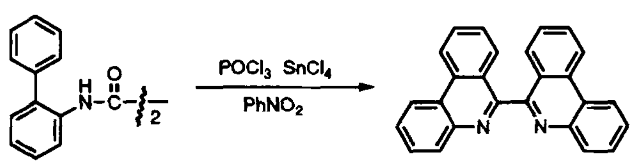
There are two possible doubly benzo-annelated bipyridines directly linked through the heterocyclic rings, and both are known. 9,9′-Biacridine (**137**) is readily obtained by the reductive coupling of 9-chloroacridine using



(137) **(138)**

a variety of reducing agents (48ZOB887; 49JCS1663; 51ZOB589), and this procedure has been used to make several other symmetrically substituted derivatives (47ZOB1124). It can also be prepared by sequential treatment of *N*-phenylanthranilic acid with phosphoryl chloride and phenylmagnesium bromide (40CB805). Attempts to prepare unsymmetrically substituted derivatives by closure of one of the rings were unsuccessful (59ZOB2652). The ^{1}H and ^{13}C NMR spectra of **137** have recently been fully assigned [93JCS(P2)757]. Zinc and hydrochloric acid reduction of **137** leads to a mixture of dihydro and tetrahydro derivatives (65JCS4657). The 10,10′-dimethyl dinitrate salt of **137** is a very well-studied chemiluminescent compound (lucigenin), which has recently been chemically converted into **137** [94JPR(336)506]. Biacridines were the subject of an early review [73CH(9)519].

6,6′-Biphenanthridine (**138**) has been prepared by reductive dimerization of phenanthridine by alkali metals, and its structure confirmed by an independent synthesis via a double Pictet–Gams cyclization of an oxamide, as shown in Scheme 46 (62JOC4171). It has also been prepared by thermolysis



(138)

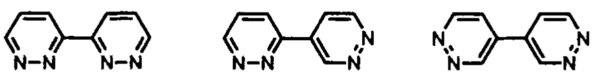
SCHEME 46

of an organogold compound, obtained by auration of 6-phenanthidinyllithium [80JOM(190)C56]. Its chemistry has not been investigated.

VI. Six-Membered Rings: Two Nitrogens

A. Bipyridazines

Of the three possible bipyridazines (**139–141**), only the 3,3′ isomer (**139**) is known. It was first prepared, in low yield, by oxidative coupling of pyridazine over palladium on carbon (67JOC1591). Better yields are ob-



(**139**) (**140**) (**141**)

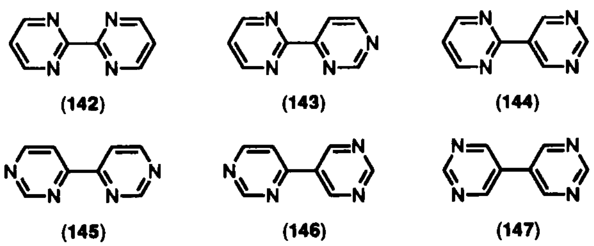
tained by palladium-catalyzed coupling of 3-chloropyridazine (69TL2359), and this has been used for the preparation of substituted derivatives (69TL2359), including unsymmetrical ones obtained from cross-couplings of two different halopyridazines (70CPB1228). A derivative of **139** with 2-pyridyl groups in the 6,6′ positions has recently been made by a nickel-catalyzed homo-coupling and shown to assemble into a 3 × 3 supramolecular lattice on reaction with silver triflate (94AGE2284). Neither the 3,4′ isomer (**140**) nor the 4,4′ isomer (**141**) is known. Substituted derivatives of **140** have been prepared as potential pharmaceuticals (89PHA598). The simplest known derivative of **141** is the 3,3′-dimethoxy derivative, which was obtained from reaction of 3-methoxypyridazine with potassium amide in liquid ammonia, in the presence of potassium permanganate (86JHC621). The 3,3′,6,6′-tetrakis(methoxycarbonyl) derivative of **141** was obtained from an unusual reaction of a tetrazine with *N*-methylpyrrole (75CZ292; 78AP728), and such compounds have been ring contracted to bipyrroles in the course of syntheses of isochrysohermidins (93JA8457, 93JA11418).

Most of the work with **139** has centered on its use as a chelating ligand in coordination chemistry, wherein it has been shown to have superior properties to 2,2′-bipyridine (**119**). Since **139** is the most basic of the chelating bidiazines, it is a strong σ donor (86JA3578) and, despite its relatively high-energy LUMO, is the second-best π acceptor of the diazines [86ICA(114)123]. Also, the absence of hydrogen atoms adjacent to the coordinating nitrogens makes this a sterically unhindered ligand. These factors combine to make **139** a strongly coordinating ligand; for exam-

ple, X-ray crystal structures of homoleptic octahedral nickel and iron complexes of **139** revealed unusually short M–N bond lengths [90ICA(178)151]. Molecular orbital calculations indicate a trans coplanar structure for **139** (88CJC1313; 91JPC7217). Experimental studies of **139** include electrochemical measurements [83CPL(97)103; 92JOM(436)367], spectroelectrochemistry [92JCS(P2)2007], photoelectron studies (91JPC7217), pK_a measurements (86JA3578), and EPR studies of its radical anion (86JPC5010) and quaternized salts [94JCS(P2)1923]. Many transition-metal complexes of **139** have been reported [70CPB1548; 80TMC321, 80TMC376; 83CL1185; 85NJC717, 85TMC419; 88JOM(340)71; 92JCS(P2)1493]. The only organic chemistry that has been reported for **139** is an early study of its *N*-oxidation and subsequent reactions of the *N*-oxides (70CPB1340) and cyanation reactions of quaternized derivatives (71CPB1297).

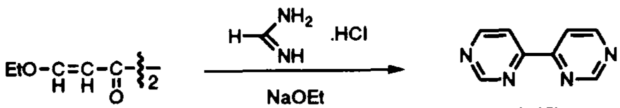
B. Bipyrimidines

a. *Synthesis.* Four of the six possible bipyrimidines (**142–147**) are known. 2,2′-Bipyrimidine (**142**), which is now commercially available, was first prepared by Ullmann coupling of 2-bromopyrimidine (62JOC2945).



(142) (143) (144) (145) (146) (147)

The yield of this reaction is somewhat variable [72OS(52)1799; 80JA611] and, as expected, is greatly improved by nickel catalysis (91SC901; 94T-11893). Various symmetrically substituted derivatives have been prepared by related homo-coupling reactions (64JOC943; 67JOC1591; 91SC901; 94AJC723), including a homochiral example (95UP2), whereas unsymmetrically substituted derivatives have been prepared by procedures involving formation of a pyrimidine ring by condensative cyclization (56JPJ772; 73JHC47; 86S786). The 4,4′-dimethyl derivative of **142** was long ago reported as a by-product in the Chichibabin reaction of 4-methylpyrimidine (39JPJ18). The 2,2′-bipyrimidine subunit has been incorporated into cryptates (89TL2209; 92HCA1221).

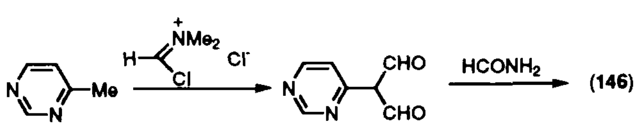


(145)

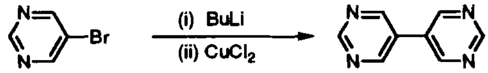
SCHEME 47

Neither the 2,4′ isomer (**143**) nor the 2,5′ isomer (**144**) is known. Substituted derivatives of **143** have been prepared by various methods, often for screening of bioactivity [67JCS(C)1204; 81AJC1353; 84AJC2093; 87JCS(P2)1551; 89CPB1984]. Many substituted derivatives of **144** have also been synthesized by condensative cyclization procedures (88KGS371; 90KGS804; 92KGS377; 93KGS509; 94KGS679). 4,4′-Bipyrimidine (**145**) was first prepared in modest yield by a double condensation as shown in Scheme 47 (65CB2260) and, shortly thereafter, by pyrolysis of the copper salt of pyrimidine-4-carboxylate, again in low yield (67JOC1591). It can be prepared directly from pyrimidine by reaction with palladium on carbon (74YZ12), by electrochemical coupling and oxidation (88NJC761), or, better, by reaction with lithium diamides (95JOC3781). Many symmetrically substituted derivatives of **145** have also been prepared by homo-coupling reactions [41JPJ99; 65JHC202; 67JCS(C)1204; 79CPB193, 79JOC2081; 81H(16)965; 93S478; 94NJC701].

The 4,5′ isomer (**146**) is the only known unsymmetrical, unsubstituted bipyrimidine. It was first prepared, as shown in Scheme 48, by cyclization of a malondialdehyde [70LA(737)46] and subsequently from 5-bromopyrimidine by lithium–halogen exchange, coupling with pyrimidine, and oxidation (79AGE1). Substituted derivatives of **146** have been prepared by butyllithium-induced unsymmetrical couplings of 5-bromopyrimidines (65ACSA1741; 74RZC2157; 76MI2), by condensations involving modified Vilsmeier reagents (75CPB2029, 75CPB2158; 76CPB1459), and by condensative cyclizations (81AJC1353; 85KGS378). The 5,5′ isomer (**147**) was first prepared (Scheme 49) from 5-bromopyrimidine by lithiation and coupling (75AGE713; 78CB1330), but can be prepared directly by nickel-catalyzed coupling (94T11893). 2,2′-Disubstituted derivatives of **147** have been prepared by double cyclizations (71JHC743; 72JHC225; 74CCC3327), whereas other derivatives have been made by various incidental methods [61JCS3345; 67JCS(C)1204, 67JOC2376; 81AJC1353].



SCHEME 48



(147)

SCHEME 49

b. *Physical Studies.* The structure and conformation of 2,2′-bipyrimidine (**142**) have been the subject of numerous experimental and computational studies. A gas-phase electron diffraction study determined a torsional angle of 49° between the two rings [81ACS(A)707]. Similarly, nematic phase NMR studies suggested a torsional angle of 40° [74OMR622; 80CPL(69)530], whereas solution infrared/Raman studies were interpreted in terms of a planar structure [90SA(A)705; 94SA(A)1317]. A nonplanar conformation represents a compromise between conjugative stabilization (favoring a planar structure) and repulsive interactions between the nitrogen lone pairs (favoring a nonplanar structure) and is found in most of the many theoretical studies of the structure [83MP(49)599; 85JPR(327)937; 88JCC369; 93CPL(215)40]. A room-temperature X-ray crystal structure showed a planar structure in the solid state [81ACS(A)707], which might be attributable to packing interactions. However, librational analysis of the structure suggests the possibility of a statistically disordered nonplanar structure. A low-temperature X-ray structure of the dihydrate of **142** showed a planar structure with the nitrogen atoms hydrogen-bonded to water molecules [81ACS(A)707]. Such hydrogen bonding to **142** has been the subject of infrared [92SA(A)671] and theoretical studies [82MMC-(183)801]. The X-ray crystal structure of **145** has also been reported (88NJC761) and, as expected, shows a trans coplanar orientation of the two rings, as is also observed in the crystal structures of its 2,2′-dimethyl (94NJC701) and 2,2′-dimethyl-6,6′-diphenyl (93NJC181) derivatives. In contrast, steric interactions induce a 46° twist about the inter-ring bond in the 5,5′-dimethyl derivative [93AX(C)1011]. X-Ray structures of copper complexes of substituted derivatives of **145** have also been reported (95IC5205).

There have been many other physicochemical and spectroscopic studies of 2,2′-bipyrimidine (**142**). These include NMR studies of all three nuclei [84OMR201; 85ICA(102)L33; 89IC1596; 90IC1761]; ultraviolet, infrared, and Raman studies [90IC1761, 90SA(A)705; 94IC2132]; photoelectron spectroscopy [82JA4571; 83MP(49)599]; electrochemical [91ICA(181)-15, 91JEC(313)243; 92IC555] and spectroelectrochemical [91JOC4678; 92JCS(P2)2007] studies; EPR studies of the radical anion [84IC3365; 91ZAAC(593)147]; pK_a measurements [87JCS(F1)3415; 89IC4251]; and

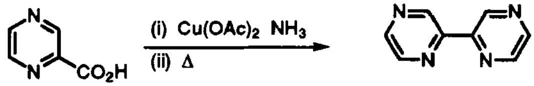
molecular orbital calculations (80TMC376; 86JA3578; 87IC68; 94OM979). Most of this work has been carried out in connection with the use of **142** as a ligand for coordination to metals. This ligand can chelate to a single metal [89CCR(93)205; 95IC5183] or to two metals separated by 5.5 Å and therefore capable of showing strong metal–metal interactions [90CCR(106)227; 95ICA(229)143]. Many mononuclear, homobinuclear, and heterobinuclear complexes of **142,** too numerous to list here, have been prepared and many X-ray crystal structures reported (e.g., 91IC157, 95IC408, 95IC4756).

Although all six bipyrimidines have been the subject of theoretical calculations [83MP(49)599], the only other well-studied compound in this series is the 4,4′ isomer (**145**), which is also a chelating ligand. Investigations of this compound include NMR studies (86JA3578), electrochemical and spectroelectrochemical measurements [88JOM(340)71; 92JCS(P2)2007, 92JOM(436)367], photoelectron spectroscopy (82JA4571), EPR measurements (86JPC5010), and theoretical calculations (80TMC376; 86JA3578; 88CJC1313, 88JCC369; 94JPC6287). Of the four chelating bidiazines, **145** has the lowest-energy π^* orbital and hence is the most easily reduced, and its metal complexes have very low-energy MLCT states.

c. *Reactions.* Surprisingly little reaction chemistry has been reported for the bipyrimidines. In connection with the incorporation of **142** as a subunit into multidentate complexing agents for lanthanoids, various methyl group functionalizations and *N*-oxidations were reported (92HCA1621). A study of the photoreduction of **142** has been reported (95JPC2343), as has an investigation of the relative reactivity of halogen-substituted derivatives of **146** (79KGS821). Quaternized derivatives of **145** have been studied [90JCS(F)3337]. Reaction of **147** with LDA produces both linear and cyclic quaterpyrimidines (75AGE713; 78CB1330).

C. Bipyrazine

There is only one possible bipyrazine (**148**). This compound, which is now commercially available, was first prepared (Scheme 50) by pyrolysis of the copper salt of pyrazine-2-carboxylic acid (64JCS1187; 67JOC1591); modifications have since improved the yield of this reaction (82IC2276; 83IC1617). It has also been prepared by a nickel-catalyzed coupling reaction (94T11893), whereas many symmetrically substituted derivatives have been prepared by various homo-coupling procedures [30MI1; 71JCS(C)3605; 74JCS(P1)2580; 82H(17)151]. Substituted derivatives of **148** have also been



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SCHEME 50

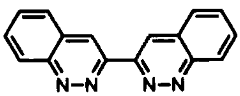
reported to result from a Maillard-type reaction of sucrose with ethylenediamine (64MI2). The 2,2′-bipyrazine subunit has also been incorporated into larger tripodal complexing agents [95TL865].

Although the crystal structure of **148** itself has not been reported, the 6,6′-dimethyl derivative has been the subject of an X-ray crystal structure determination and shown to exist in a planar transoid conformation in the solid state (94NJC701). Infrared and Raman studies suggest that **148** has a planar transoid structure in solution [94SA(A)357], and this conformation is reproduced by theoretical calculations (88CJC1313). Again, most of the interest in **148** has related to its ability to act as a chelating ligand, and numerous transition-metal complexes of **148** have been reported (64JCS1187; 80JA7128; 82IC1027, 82IC2276; 83IC822, 83IC1617; 84OM1241; 86IC176, 86JA2568; 87AGE567; 89IC3675; 94CL2443, 94POL1817; 95IC3093, 95IC5205), along with some X-ray structures (90MI1; 93AGE880, 93JA8221). In this context there have been many studies of the properties of **148**, including pK_a measurements (83JA1170; 86JA3578), electrochemical studies [84JEC(175)229; 88JOM(340)71; 92JEC(327)327, 92JOM(436)367; 94JCS(P2)1923], spectroelectrochemistry [84MI3; 92JCS(P2)2007], EPR studies [86JPC5010; 94JCS(P2)1923], UV and photoelectron spectroscopy [72MI1; 90CPL(172)151; 91JPC7217], and molecular orbital calculations (80TMC376; 87JA4149). Compared to 2,2′-bipyridine, this ligand has a very low-energy π^* LUMO, but this is somewhat offset by the ligand being a weaker σ donor. It has been shown to exist as a single-electron-transfer π acceptor from a titanium complex [92JCS(P2)1493], but the organic chemistry of **148** is totally unexplored.

D. BENZO DERIVATIVES

1. *Bicinnolines*

There are three possible bicinnolines (**149–151**). The 3,3′ isomer (**149**) has been prepared in high yield by a palladium-catalyzed coupling of 3-



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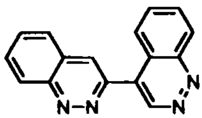

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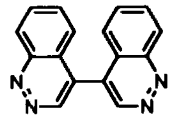
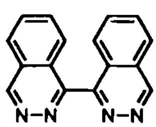


(151)

bromocinnoline (82T383). Neither the 3,4′ isomer (**150**) nor any simple substituted derivative is known. The 4,4′ isomer (**151**) has been prepared by a number of methods. It was first made by decarboxylation of cinnoline-4-carboxylic acid and by Busch coupling of 4-chlorocinnoline, both in low yield (51JCS1971). It has also been obtained in low yield from attempted phenylation of cinnoline (59JCS3040) and an attempted acylation of 4-methylsulfonylcinnoline (70JPP70/19908). Better yields are obtained by lithium aluminium hydride reduction of 4-chlorocinnoline (62JCS1509) or by hydrolysis (Scheme 51) of a Reissert-type intermediate obtained from cinnoline (80JHC1211). The 3,3′-dicyano derivative has similarly been prepared by catalytic hydrogenation of 4-chloro-3-cyanocinnoline [76JCS(P1)-592]. Apart from a mass spectrometry and NMR study of **151** (68JHC639), the structures and properties of these compounds have not been investigated.

2. *Biphthalazine*

Surprisingly, 1,1′-biphthalazine (**152**) itself has not been reported. The simplest known derivatives are the 4,4′-diphenyl derivative, which was



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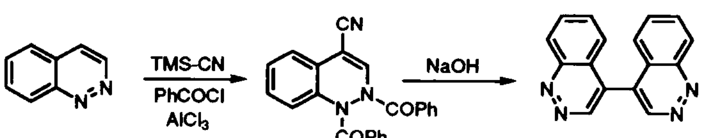

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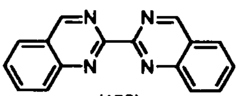
SCHEME 51

obtained as a by-product from an attempted acylation of 1-methylsulfonyl-4-phenylphthalazine (67YZ807), and the 4,4′-dihydroxy derivative, which was produced by condensation of hydrazine with diphthalic acid (66T1309). Reduced derivatives of **152** are known, and these ought to form **152** on oxidation. For example, a tetrahydro derivative is obtained from phthalazine by photolysis (74BCJ1257; 84CL1901; 88BCJ893; 91BCJ3340) or by treatment with organometallic reagents [82JA4298; 93JOM(451)169]. A dihydro derivative is formed by thermolysis of 1-hydrazinophthalazine (76MI3).

3. *Biquinazolines*

There are three possible biquinazolines (**153–155**), two of which are known. The 2,2′ isomer (**153**) is readily prepared by condensative cyclization of an oxanilide, as shown in Scheme 52 (65JCS1258). This procedure had



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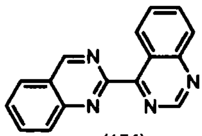

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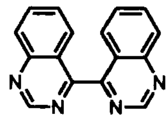
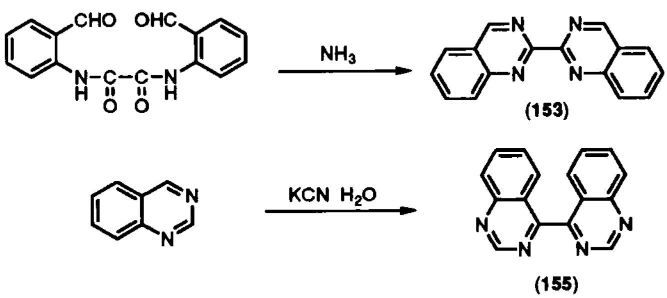


(155)

earlier been used to prepare 4,4′-disubstituted derivatives (54JCS4034). The 4,4′-diphenyl derivative has been prepared by both single and double cyclizations (86T3697), whereas the 4,4′-dihydroxy derivative has been made by palladium-induced coupling of 4-quinazolone (76YZ8). The 2,2′-biquinazoline group has also been incorporated into a macrocycle used as



SCHEME 52

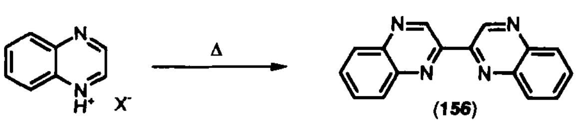
a model for dicyanocobalamine (88IC4645). A substituted derivative of **153** has been identified as the fluorescent acid-hydrolysis product of the tranquilizer oxazepam [79CCC2243; 93JCR(S)304].

The 2,4′ isomer (**154**) has not been reported, the simplest known derivative being the 4-hydroxy derivative, obtained by treatment of 4-quinazolone with sodium naphthalenide (94T9079). 4,4′-Biquinazoline (**155**) was first prepared, in low yield, from the reaction of 4-chloroquinazoline with Grignard reagents (62CPB1043), but is best prepared (Scheme 52) by treatment of quinazoline with aqueous cyanide (65JCS1258; 74CPB2493). It can also be prepared from quinazoline by various other methods (72CPB1544; 77JOC78), including reactions of Reissert-type intermediates (85JHC1313). Substituted derivatives have been prepared by miscellaneous cyclization or coupling methods [77AGE727, 77JOC78; 84JCS(P1)1143].

The X-ray crystal structure of **153** has been determined (91UP1), and this showed a planar transoid conformation. The structure of a reduced (octahydro) derivative of **153** has been reported [94JCS(P2)421]. A UV study (74MI3) and the preparation of copper complexes (70UKZ652) have been reported. The ^{1}H and ^{13}C NMR spectra of **153** have been fully assigned as part of an investigation of binuclear complexes of **153** (94UP1). The ^{1}H and ^{13}C NMR spectra of **155** have also been reported (85JHC1313). The only reaction chemistry reported for these compounds is the oxidation of **155** to 4-quinazolone (85JHC1313).

4. *Biquinoxaline*

2,2′-Biquinoxaline (**156**) was first prepared by a condensative cyclization for formation of one of the rings (38CB2092). It has since been prepared directly from quinoxaline by treatment with sodium amide (46NAT439), palladium on carbon (62JOC2679; 78YZ67), cyanide ion (76CPB238), and, in what appears to be the best method (Scheme 53), by heating of quinoxalinium salts (76ZOR2464). Monosubstituted derivatives of **156** have been prepared by single cyclization procedures (66JHC367; 69CB1418; 72KGS1289; 73TL1105), whereas symmetrically substituted derivatives have been made by double cyclizations (62JOC2679; 58M570), by homo-



SCHEME 53

coupling reactions (93JHC1491), by ring openings of cyclobutenediones (76LA284; 77CB2506), and by reactions of *o*-phenylenediisonitriles with organometallic reagents [90JA6446, 90JCS(CC)403]. The 3,3′-bonded derivative, diquinoxalylene, has been prepared from squaric acid (72AGE433) and its X-ray crystal structure determined (74CSC57).

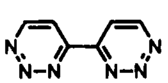
Physical studies of **156** include a UV study (74MI3), electrochemical studies [84JEC(179)209; 92JEC(327)327], spectroelectrochemistry [85JEC-(193)205], pK_a measurements (87PJC467), phosphorescence measurements (84JPC3982), and photoreduction studies (87M659). 2,2′-Biquinoxaline is readily reduced to a highly colored dihydro derivative, and this has been exploited in several spectrophotometric methods of analysis (88MI4, 92TAL1205; 93MI9; 94MI3, 94MI4, 94TAL1161). The organic reaction chemistry of **156** was the subject of a very early study (38CB2092).

VII. Six-Membered Rings: Three or More Nitrogens

A. Bitriazines

1. *Bi-1,2,3-triazines*

None of the three possible isomers (**157–159**) is known. A hexamethyltetrahydro derivative of **159** has recently been reported [92H(33)631], while



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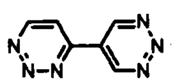

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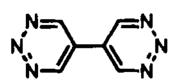

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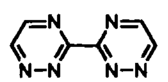

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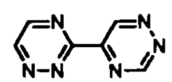

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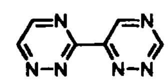

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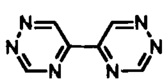

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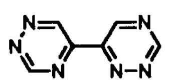

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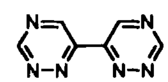

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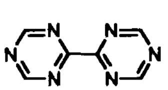

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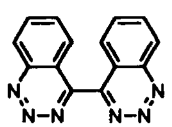

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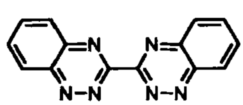

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the conformation of **159** itself has been the subject of theoretical calculations (86IJQ541).

2. *Bi-1,2,4-triazines*

Of the six possible isomers (**160–165**), only two of the three symmetrical isomers, and some of their substituted derivatives, have been reported. The 3,3′-isomer (**160**) has been prepared by reaction (Scheme 54) of glyoxal with oxalamidrazone (36MI1); by the use of appropriate α-dicarbonyl precursors, this procedure has been extended to the syntheses of many symmetrical di- and tetrasubstituted derivatives [57T(1)103; 65JOC931; 67JHC422; 71JPR(313)699; 78JFC439; 84ACA(161)231]. The coordination chemistry of some of these substituted derivatives has also been studied [64MI1; 65ACA(32)235; 94MI19]. The 5,5′,6,6′-tetraphenyl derivative of **160** has been the subject of a recent X-ray crystal structure determination [93AX(C)1541].

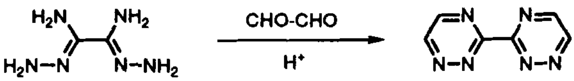
The 5,5′ isomer (**163**) is readily prepared (Scheme 55) by treatment of 1,2,4-triazine with cyanide ion (74JHC43). Various substituted derivatives have been prepared by related dimerizations induced by cyanide, base, or free radical species [67YZ1501; 73BSF2493, 73JHC343; 75RTC204; 82JHC653; 86H(24)1243; 87CPB1378]. The only reaction chemistry described for these compounds is an isolated report of Diels–Alder reactions of the 3,3′-dimethoxy derivative of **163** with a reactive dienophile (77LA1413).

3. *Bi-1,3,5-triazine*

This compound (**166**) has not been reported. Tetrasubstituted derivatives have been prepared, in low yields, by Ullmann couplings of the corresponding iodotriazines (82NKK1425), while a tetrahydro derivative has been reported to result from the electrochemical reduction of 1,3,5-triazine (86JES2509).

4. *Bibenzotriazines*

Neither of the two possible bibenzotriazines, **167** or **168**, has been reported.



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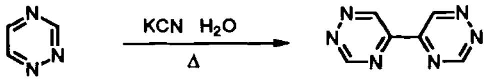
SCHEME 54



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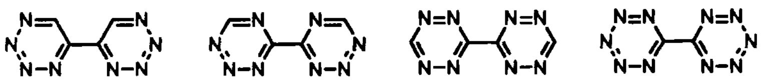
SCHEME 55

B. OTHER SYSTEMS

None of the three possible bitetrazines (**169–171**) has been reported, although all three isomers have been the subject of *ab initio* and AM1 semiempirical calculations (92MI5). The only simple substituted derivative



(169) (170) (171) (172)

of any of these compounds to have been reported is the 6,6′-diphenyl derivative of **171.** This was first described (90KGS1691) to result from the elimination of nitrogen from the corresponding azotetrazine. However, this would seem to be incorrect in view of a more recent alternative five-step synthesis, which produced a product with different properties (94TL7935). This compound was also shown to be a reactive diazadiene in Diels–Alder reactions (94TL7935).

Since pentazine itself is not known, it is hardly surprising that bipentazine (**172**) has not been reported.

ACKNOWLEDGMENTS

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1,2,4-Triazoline-3,5-Diones

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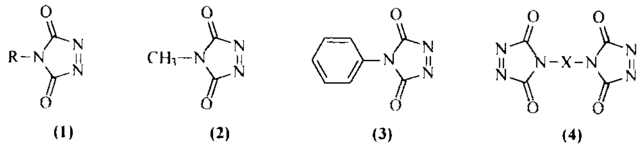
I. Introduction

A review on azodicarbonyl compounds, which contain a carbonyl function on both sides of the azo bond, was published in this series in 1982 and covered the main aspects of this type of heterocyclic compounds [82AHC(30)1]. A more recent review on mono- and diazaquinones updates



SCHEME 1

the sections dealing with six-membered diazaquinones [94AHC(61)141]. However, the corresponding five-membered cyclic azodicarbonyl compounds have not been reviewed recently. The only relatively comprehensive review was published in 1983 in Russian (83KGS147). We now present a brief treatment of the chemistry of 1,2,4-triazoline-3,5-diones (TADs) **1,** the most widely used compounds of this type. Literature coverage, though not exhaustive, is reasonably complete to the end of 1995.

The most frequently used 1,2,4-triazoline-3,5-diones include 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) (**2**) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**3**), also called the Cookson reagent. Many other substituted derivatives of PTAD are also known but not widely used. A similar situation is found with some bifunctional compounds **4,** where X can be aliphatic, aromatic, or a combination of aromatic and aliphatic parts [72MI1; 78CB3519; 79MI1, 79MI2; 85MI1; 87JPS(A)2781].

II. Experimental Structural Methods

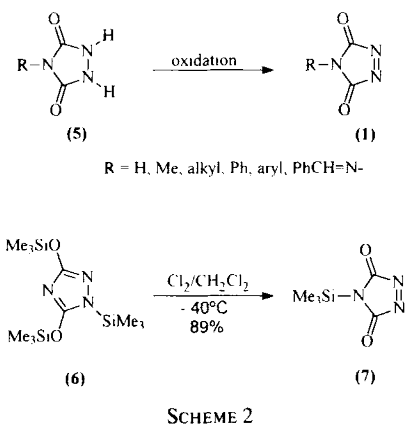
UV spectroscopy has been used to demonstrate the predominantly dioxo structure of PTAD [UV spectrum (dioxane), λ [nm] (ε): 247 (2300), 310 (1020), and 532 (171)] [71OS121; 88OSC(6)936]. The IR spectrum of PTAD has also proved the dioxo structure [IR spectrum [cm^{-1}]: 1760 and 1780] [71OS121; 88OSC(6)936]. He(I) photoelectron spectra of MTAD and PTAD have been correlated with data obtained by MO calculations (MNDO, INDO, STO-3G) (85JOC4375). Various aspects of the decay of the excited electronic state of MTAD have been studied (74JCP2779, 74JCP3587).

III. Synthesis and Stability

1,2,4-Triazoline-3,5-diones are generally prepared by oxidation of the corresponding urazole derivatives **5** with lead tetraacetate (LTA) (67JOC330) or *t*-butyl hypochlorite [62TL615; 67JCS(C)1905]. Most TADs, including the *N*-4 unsubstituted 1,2,4-triazoline-3,5-dione, have not been isolated, but can be generated and reacted *in situ*. Other oxidants which have

been used for the preparation of TADs include lead dioxide (1894LA1), nitrogen dioxide (66JOC3444; 82S159; 92JCE238], *N*-bromosuccinimide (75OPP251), DDQ, activated manganese dioxide, barium manganate [96JCS(P1)167], *p*-toluenesulfonyl isocyanate or benzoyl isocyanate with DMSO (74JOC3799), and benzeneseleninic anhydride [78JCS(CC)276; 83TL2995]. Two methods of electrooxidation of urazoles to the corresponding TADs have also been described (81AG832). Hypervalent iodine oxidation of phenylurazole using iodobenzene diacetate gives high yields of PTAD (87SC409). This mild and nonacidic method could be useful in the preparation of TADs bearing sensitive substituents. *N*-Trimethylsilyl TAD (**7**) can be prepared by oxidation of **6** with chlorine in dichloromethane at −60°C (88AG703). The preparation of TADs is only occasionally complicated with an additional reaction. The only important example is oxidation of 4-(4-hydroxyphenyl) urazole, which can be achieved in the usual way with *t*-butyl hypochlorite, and which gives a good yield of 4-hydroxy-3-nitrophenyl TAD when nitrogen dioxide is used as an oxidant (87CB691).

Most TADs are not stable and are usually formed *in situ*. However, Sauer and Schröder (67CB678) isolated PTAD in crystalline form in 50% yield by oxidation of 4-phenylurazole with bromine. A more efficient synthesis using *t*-butyl hypochlorite in ethyl acetate provides PTAD in 62–64% yield [71OS121; 88OSC(6)936]. Crystalline PTAD can be purified by sublimation and forms carmine-red crystals which decompose before melting at 165–175°C. The compound prepared in this way has a shelf life of several months if stored in the dark in a refrigerator. The same method was used also for the preparation of 4-methyl-, 4-*t*-butyl-, 4-(4-nitrophenyl)-, and 4-benzalamino-1,2,4-triazoline-3,5-diones [71OS121; 88OSC(6)936]. PTAD is now also commercially available, e.g., from Aldrich. TADs prepared by usual procedures are contaminated with free radicals, which cannot be



SCHEME 2

removed by sublimation or recrystallization (82JOC1459). Some of the reactions of these compounds are explained by the presence of these radicals.

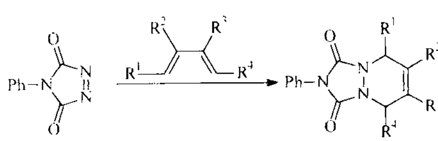
IV. Reactions

Although some 1,2,4-triazoline-3,5-diones can be isolated, these reagents are generally formed *in situ* as mentioned earlier. TADs undergo several types of addition reactions to alkenes and/or dienes, for example, [2+4] Diels–Alder additions, homo Diels–Alder additions, ene reactions, and [2+2] additions. The adducts, in many cases, can be further used for a wide variety of chemical transformations. TADs also add to a wide range of organic compounds to give polycyclic urazoles. Very often several possible reactions compete, and under different conditions the composition of such reaction mixtures often differs. It is necessary to say that even the presence of a reactive diene system does not entirely eliminate the possibility of [2+2] addition and/or ene reaction as documented in the appropriate sections.

A. Diels–Alder Reaction

1. *Cycloadditions of Butadiene Derivatives*

PTAD is well known as a powerful dienophile that reacts intermolecularly with various dienes at −78 to −50°C, as evidenced by the immediate discharge of the red color (62TL615; 70TL2407). Its reactivity is about 10^3 higher than that of TCNE, one of the most powerful dienophiles (80JOC1232). There are many examples of the Diels–Alder addition of TADs, especially PTAD, to various dienes. Selected examples are given in Table I. The reaction generally provides high yields of the 1,4-adducts and is often used for intercepting labile dienes of natural origin and/or for their structure elucidation (see Section IV,A,6). Generally, such Diels–Alder adducts can be easily hydrogenated to the corresponding hexahydropyridazine derivatives (69CB811; 91JOC613) or transformed to the



Scheme 3

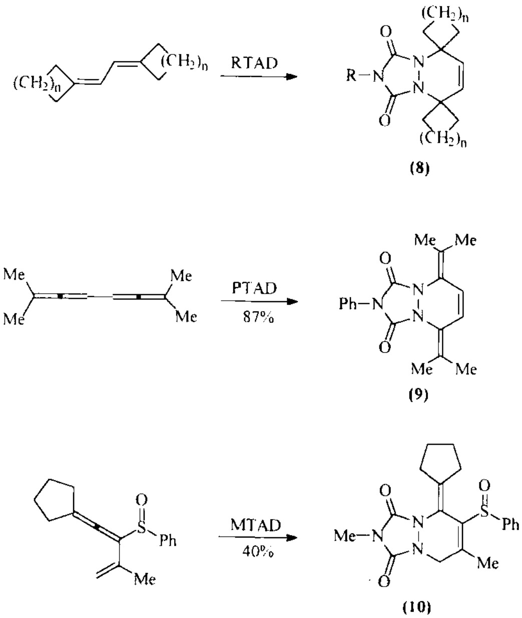
TABLE I
REACTION OF PTAD WITH DIENES (SCHEME 3)

R^1	R^2	R^3	R^4	Yield (%)	Ref.
H	H	H	H	—	62TL615
				61	67JCS(C)1905
Me	H	H	H	96	87JA6376
H	N_3	N_3	Me	92	87AG932
COOH	H	H	H	93	76JCS(P1)2390
MeO	H	MeO	H	82	82JOC4774
Me	H	H	$(CH_2)_3SePh$	89	90JOC1786
H	Me_3SiO	Me_3SiO	H	90	88CB185
Ph	H	H	$C[P(O)(OMe)_2]=N^+=N^-$	72	85T2625
Ph	H	H	Ph	—	79ZOR361
H	PhS	PhS	H	—	85PS(24)305
$-CH_2-CH_2-O-$		Ph	H	38	90TL6077
$-CH_2-CH_2-CH_2-O-$		Ph	H	46	90TL6077
$-O-CH_2-CH_2-O-$		H	H	79	86CB3204
$-O-CH_2-CH_2-CH_2-$		H	H	84	86CB3204

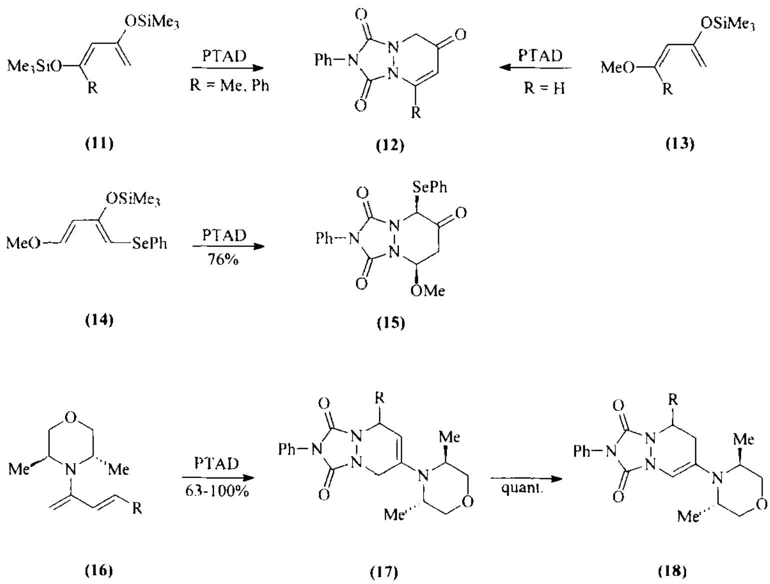
corresponding dihydropyridazine derivatives by a bromination and bis-dehydrobromination procedure (85JOC5604).

Dicyclopropylidenethane (84JOC3618; 85BCJ1603) and dicyclobutylidenethane (85JOC3485) provide with TADs the usual Diels–Alder adducts **8** in variable yields ranging from 17 to 74%. Allylidene cyclopropanes with PTAD give analogously the corresponding spiro compounds (71JA440; 91TL3483). Interesting bicyclic structures containing two exocyclic double bonds, e.g., **9**, are formed in the Diels–Alder reaction of 1,2,4,5-hexatetraenes with PTAD [78JCS(P1)1568; 81LA165]. MTAD reacts at subambient temperatures also with vinylsulfoxyallenes to give the corresponding Diels–Alder adducts, e.g., **10** (94JHC871).

PTAD reacts also with the electron-rich diene 1,3-dimethoxy-1,3-butadiene and provides the corresponding adduct in 82% yield (82JOC4774, 82TL2155). 1,3-Bis-dimethylsilyloxy-1,3-butadienes (**11**) react rapidly at room temperature to give enones **12** (R = Me, Ph) in good yields (87CB1597) after workup. The same type of enone bearing R = H is obtained in 84% yield from 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**13**) similarly [79JA7001; 85JCS(P1)71]. The corresponding phenylseleno derivative **14** provides **15** similarly (77JOC1819; 79JA7001). 2-Morpholino-1,3-butadiene **16** reacts with PTAD to give adduct **17**, which then isomerizes to the more stable isomer **18**, where two nitrogen atoms are in conjugation with the double bond (Scheme 5) (94S66).



SCHEME 4



SCHEME 5

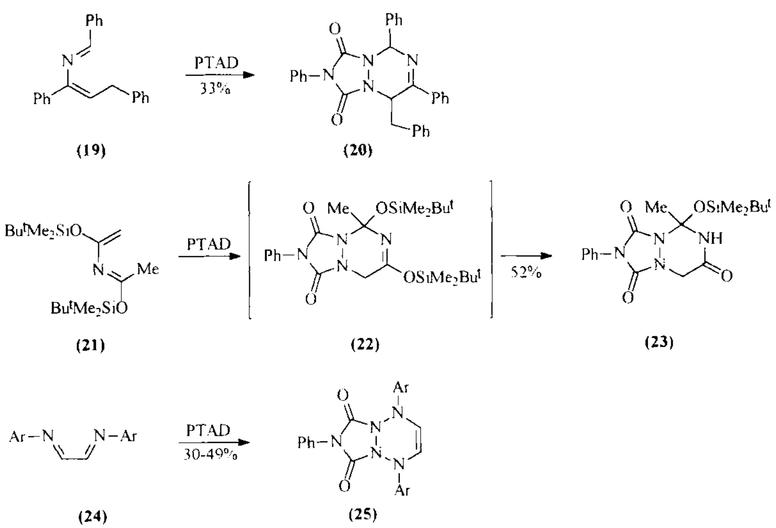
Triphenyl azapentadiene **19** treated with PTAD gives Diels–Alder adduct **20** (75CJC355). Azapentadiene **21** reacts with PTAD via the Diels–Alder adduct **22,** which, in this case, cannot be isolated, giving bicyclic lactam **23** (87HCA1255). The usual Diels–Alder reaction has been described for some other 2-aza-1,3-dienes as well [89JCR(S)66]. Diels–Alder reaction of PTAD with diazadiene **24** provides **25** [82IJC(B)589].

Compounds containing two adjacent exocyclic methylene groups usually give products of Diels–Alder addition (76JA1875; 77LA27; 81TL2579). Examples of such three-, e.g., **26,** (86JOC2122), four-, e.g. **27** (76JA1875; 79TL2351), and five-membered compounds, e.g., **28** (77LA27; 79CB862) have been published (Scheme 7). In the case of **29,** the Diels–Alder adduct **30** can be further rearranged with the loss of sulfur dioxide to afford tricyclic compound **31** [85JCS(CC)1785].

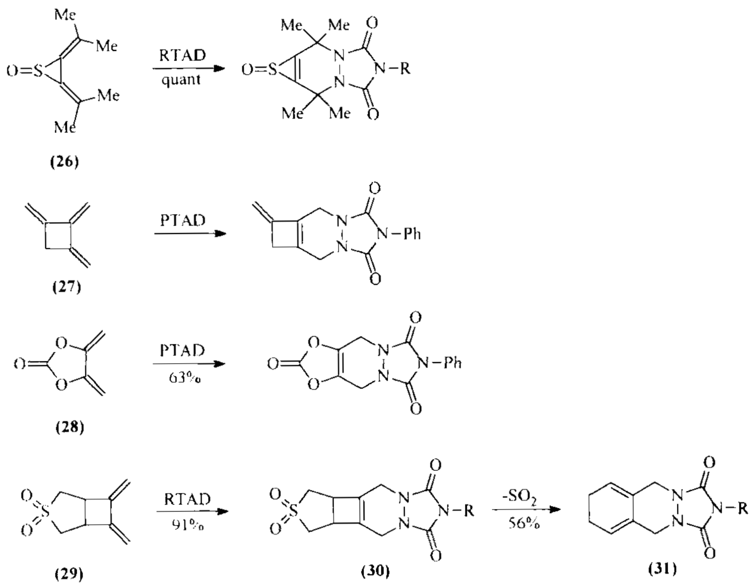
Diels–Alder adduct **33,** formed from dimethylenenorbornenone **32,** eliminates carbon monoxide on warming to room temperature to give aromatic derivative **34** [84JCS(CC)1675]. Dimethylenenorbornene **35** (81TL2579) and ethanoanthracene **37** (79ZOR2367) give quantitatively adducts **36** and **38,** respectively (Scheme 8).

2. *Additions with Cyclic Dienes*

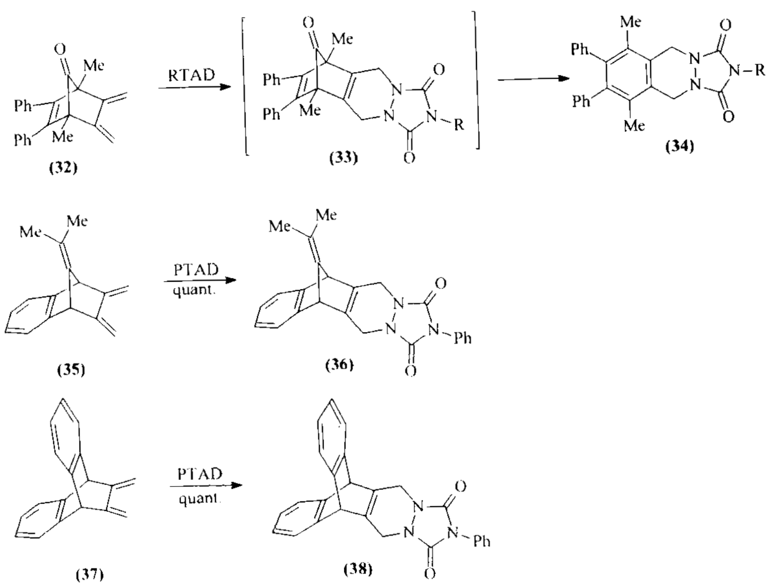
TADs usually react with cyclic conjugated dienes **39** to give the corresponding Diels–Alder adducts **40.** PTAD reacts with cyclopentadiene at



SCHEME 6



SCHEME 7

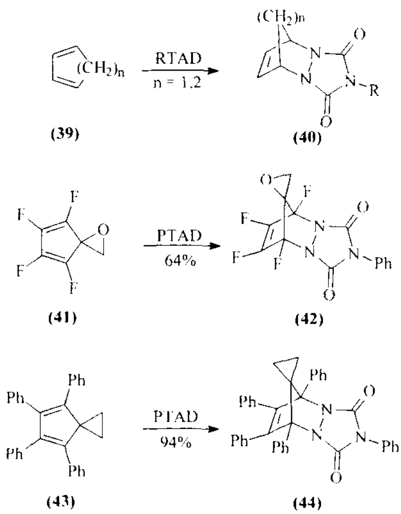


SCHEME 8

−78°C to give the corresponding product of [2+4] cycloaddition (62TL615; 73TL2101; 74JA5158). The same reaction has also been observed with some cyclopentadiene derivatives, e.g. 5,5-dimethoxy-1,3-cyclopentadiene (76CB1577). Sterically crowded 1,2,3,4-tetraphenyl-1,3-cyclopentadiene as well as the corresponding cyclopentadienone give with PTAD nearly quantitative yields of the Diels–Alder adducts (73LA129). As in the case of cyclopentadienes, 1,3-cyclohexadiene derivatives give the corresponding Diels–Alder adducts, usually in good yields [74JA5158; 79JCS(CC)36, 79TL779; 80S238]. Crystal structures of a series of cyclopentadiene and cyclohexadiene adducts have been reported (86JA4477). PTAD reacts at 110°C even with extremely unreactive 1,2,3,4,5,6-hexafluoro-5,6-dichloro-1,3-cyclohexadiene (89JOC5511).

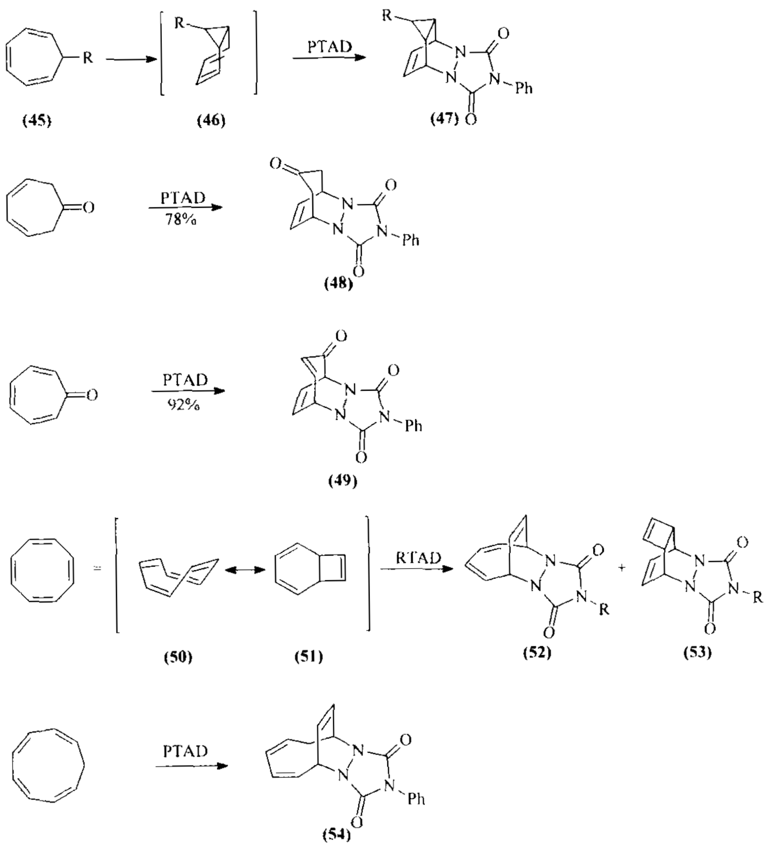
Spiro compounds **41** (91JOC157) and **43** (78LA1648) treated with PTAD give good yields of the Diels–Alder adducts **42** and **44,** respectively.

Cycloheptatriene derivatives **45** react with PTAD in the form of norcaradiene isomers **46** to give 1,4-cycloadducts **47** [62TL615; 67JCS(C)1905; 69JA777; 77CJC251; 79JA6285; 82CB3427; 86CB3704; 87CB2075]. On the other hand, reaction of 3,5-cycloheptadien-1-one (79JOC861) and tropone [71JCS(C)2142] gives the Diels–Alder adducts **48** and **49,** respectively. Tropone ethyleneketal (85CB332), as well as a similar *N*-oxide of cycloheptatrienylidenemethylamine (78JA1954), reacts in the same way. 1,2-Benzocycloheptatriene treated with PTAD gives exclusively the corresponding cycloheptatriene Diels–Alder adduct (84TL4033; 86T1461).



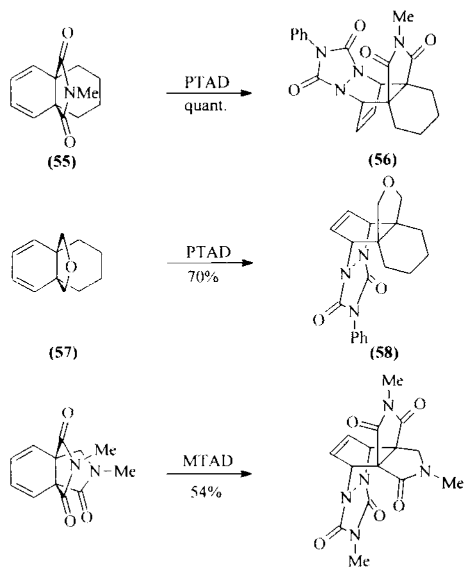
SCHEME 9

Several studies on the reaction of cyclooctatetraene with TADs have been published. Usually both isomers **50** and **51** are involved in the reaction giving a mixture of **52** and **53**, respectively [67JCS(C)1905; 68TL5863; 70JA4105, 70JA5765; 71CB2405; 72AG765; 76TL2355; 77TL889; 79AG-578; 80CB2154; 82TL2837]. Similar reaction of a complex of cyclooctatetraene and iron tricarbonyl with MTAD gives the corresponding derivative **52** and a barbaralene derivative [77ACS(B)635; 78JA285]. 3,5,7-Cyclooctatriene-1,2-dione gives with PTAD a corresponding Diels–Alder adduct (77CL293). All-cis cyclononatetraene derivatives give with PTAD exclusively products of 1,4 addition, e.g., **54** [69TL4491; 70TL911; 72JCS(CC)92].



SCHEME 10

Reactions of PTAD and MTAD with a wide range of cyclohexadiene rings containing propellanes have been extensively studied [72T2315; 73T2373; 74T3415; 76H(5)25, 76T1013; 77JA2815, 77T1169, 77T1177, 77T1183; 79BSB841; 80T3209; 81T127; 89IJC281; 90JOC1598; 91AJC555]. The reaction of some heterocyclic propellanes is shown in Scheme 11. In principle, the dienophiles can approach the propellane system from "above," i.e., from the side of the ring containing a heterocyclic atom, or from the opposite side "below" the cyclohexadiene ring, and consequently a mixture of both possible isomers is often formed. However, in some cases, especially with heterocyclic propellanes, only one of the possible isomers is formed. Both steric and electronic factors seem to be involved. With propellane **55,** the attack from the "above" side is preferred, probably because of an interaction of the CO π orbitals with the nitrogen atoms of PTAD; **56** is formed exclusively. Compound **57** lacking the carbonyl groups gives exclusively **58,** the product of the attack from the "below" side (74T3415). Unlike propellane **55,** similar [4.3.3]propellane **59** gives exclusively **60,** the product of attack from "below" (89IJC281). Structures of some of these adducts have been determined by X-ray spectroscopy [92AX(C)1479].



(55) (56) (57) (58) (59) (60)

SCHEME 11

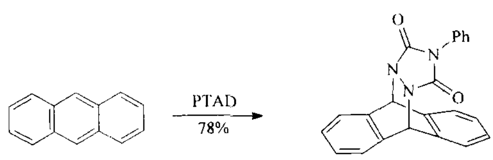
3. *Additions with Aromatic Compounds*

Diels–Alder addition of MTAD to naphthalene (84JA5368; 85MI2) and phenanthrene (88TL5509) under photochemical conditions has been described. Even irradiation of an MTAD solution in benzene at −40°C gives the corresponding Diels–Alder adduct (89JA9247). However, these adducts are thermally unstable and undergo cycloreversion at about −10°C.

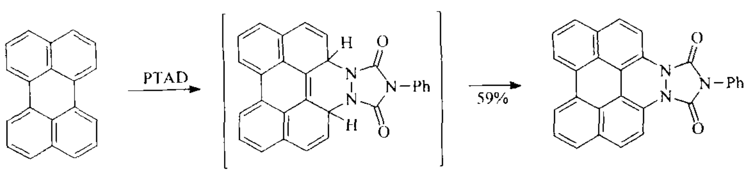
TADs react with anthracene to provide products resulting from addition onto the C-9,10 positions, as revealed by structure **61** formed from PTAD [67CB678, 67JCS(C)1905; 75JCS(P2)1325; 79ZOR361]. The analogous reaction has been documented for various diazaquinones as well [94AHC(61)141].

PTAD reacts with perylene to provide polycyclic derivative **63,** probably via Diels–Alder adduct **62,** which is further stabilized by oxidation to the final product (74CB1406). Similar addition of PTAD to naphtho[1,2,3,4-*def*]chrysene and other polycyclic arenes has also been described (75CZ92; 88CB1647).

Interesting reactivity toward TADs has been observed for some cyclophanes, e.g., **64–66** (Scheme 13). Paracyclophane **65** treated with PTAD at 20°C gave after 3 hr a 79% yield of the corresponding 1:1 adduct **67,** and prolonged treatment (24 hr) provided a 65% yield of the 2:1 adduct **68.** The monoadduct easily disproportionated during crystallization to give the bis adduct and the starting cyclophane (80CB2358; 82AG291). Less active cyclophane **64** treated with PTAD for 138 hr gave 90% of the corresponding 2:1 adduct. However, **66,** the most reactive cyclophane of the series, gave the corresponding 2:1 adduct in 3 min (80AG388).

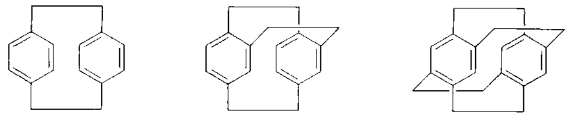


(61)

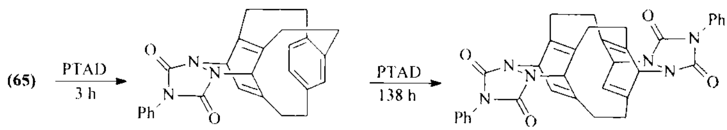


(62) **(63)**

SCHEME 12



(64) (65) (66)



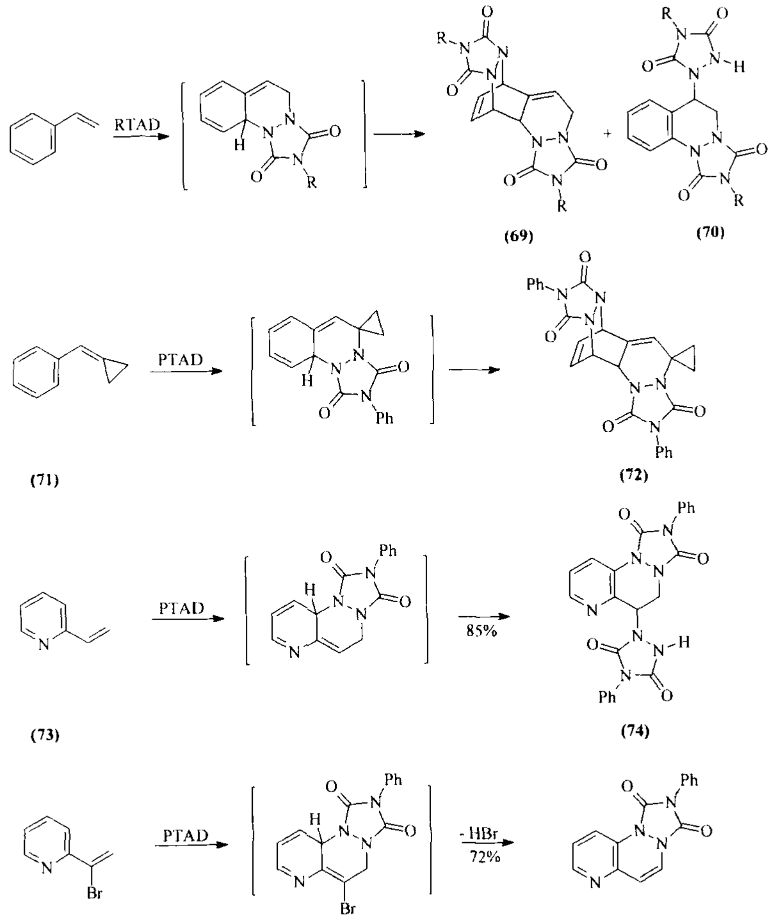
(67) (68)

SCHEME 13

Aromatic and heteroaromatic systems bearing a vinyl group usually react with PTAD via [4+2] intermediates which react with an additional molecule of PTAD to give 2 : 1 adducts either by [4+2] addition or by an ene reaction (Scheme 14). For example, addition of PTAD or MTAD to styrene and its derivatives gives a mixture of both possible 2 : 1 products. At low temperature the ene product **70** prevails, but at room temperature the Diels–Alder bis adduct **69** is formed [62TL615; 67JCS(C)1905; 77AQ1035; 79AQ749; 83BCJ2857; 85JOC4378]. Benzylidenecyclopropane (**71**) is reported to give only the Diels–Alder bis adduct **72** (72TL2995). However, 2-vinylpyridine (**73**) is reported to provide ene-Diels–Alder product **74** (76KGS702). Other workers coud not repeat this experiment (79T2027). α-Bromovinylpyridine (**75**) under similar conditions gives compound **77,** which is a product of dehydrobromination of the corresponding Diels–Alder monoadduct **76** (78KGS651).

With 2-vinylthiophene, monoadduct **78** is formed (74JA5591). Reaction of 1-phenyl-5-vinylpyrazole with PTAD gives similar tricyclic adduct **79** [90JCS(P1)2749]. However, the same reaction of 1-*t*-butyl-4-vinylpyrazole takes place exclusively through the vinyl substituent to afford **81** as the only isolated product. Formation of this product can be rationalized through the ene intermediate **80** (89M1113).

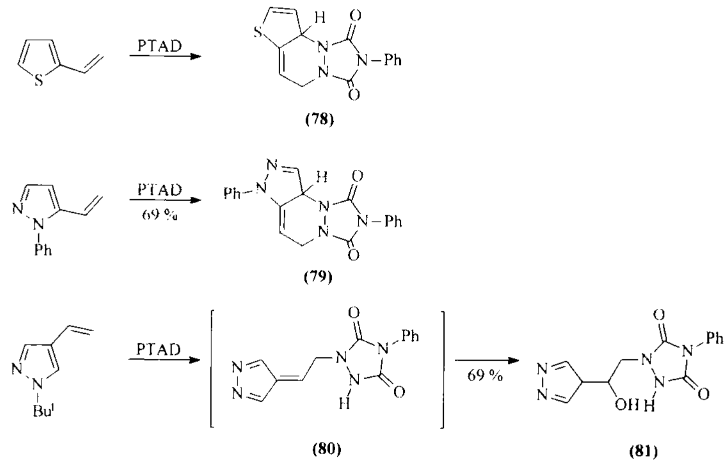
Reactions of some 2- and 3-vinylindoles with TADs have been reported. Depending on the substitution pattern of the vinylindole, Diels–Alder, Michael, or ene-type reactions, and PTAD-catalyzed dimerization are observed (87M1073; 90C339; 91CZ237, 91HCA727, 91TL1771; 92AP353). However, in some cases of both 2-vinylindoles [88H(27)967; 90C339] and 3-vinylindoles (86C124; 87M1073; 90C339; 91HCA727; 92JOC910), good yields of the Diels–Alder adducts have been obtained (Scheme 16). With 2-vinylindoles **82,** the side-chain double bond of the intermediates **83** is



(69) (70) (71) (72) (73) (74) (75) (76) (77)

SCHEME 14

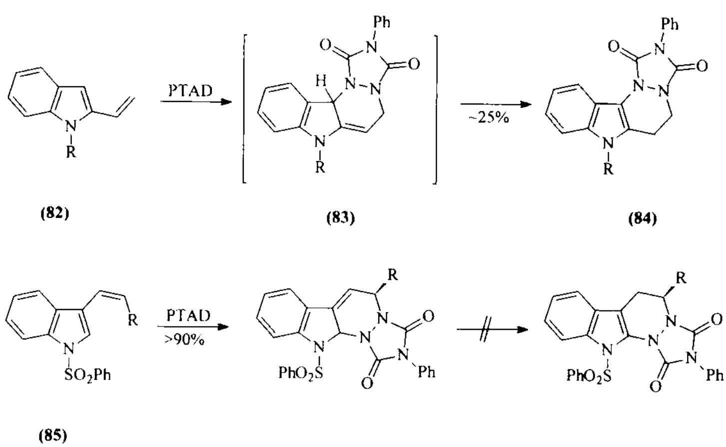
shifted to form the final products **84.** No such shift has been described for 3-vinylindoles. The course of the reaction of 2-vinylindoles is highly dependent on the substitution of the vinyl group. For example, no products of the Diels–Alder reaction have been obtained from the reaction of PTAD with 1-methyl-2-(1-substituted vinyl)indoles. Products of a Michael-type reaction were obtained instead [87H(26)401] (see Section IV,I). Examples of 3-vinylindoles which provide high yields (>90%) of Diels–Alder adducts



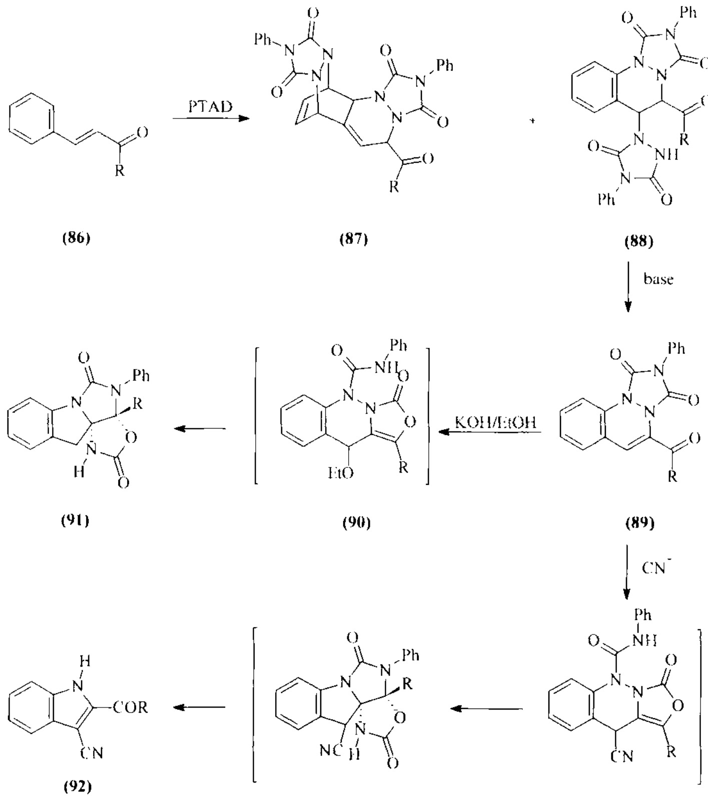
SCHEME 15

include **85** (R = H, OMe) (87M1073; 92JOC910). Interestingly, the corresponding (E) methoxy isomer gave rise to a mixture of unstable products.

Reaction of PTAD with benzylidene ketones **86** provides a mixture of two 2:1 adducts **87** and **88**, in which thermally unstable Diels–Alder-ene adducts usually prevail (Scheme 17). Treatment of this mixture or isolated adduct **88** with a base, e.g., triethylamine, causes elimination of urazole from **88**, leading to **89** [90MI1; 91BCJ3188; 91JCS(CC)89, 91JCS(P1)2883; 94JCS(P1)2335; 95JCS(P1)519]. Reaction of these tricyclic compounds with



SCHEME 16



SCHEME 17

ethanolic potassium hydroxide proceeds via opening the urazole ring by Michael addition to the enone substructure, followed by participation of the neighboring β-carbonyl group and skeletal rearrangement to the final product. Formerly published structure **90** was later found to be incorrect, and the correct structure **91** was established by X-ray crystallography [94JCS(P1)2335]. A new method of preparation of 3-cyanoindoles **92,** based on treatment of **89** (R = Me, EtO) with cyanides, has recently been described [95JCS(P1)519].

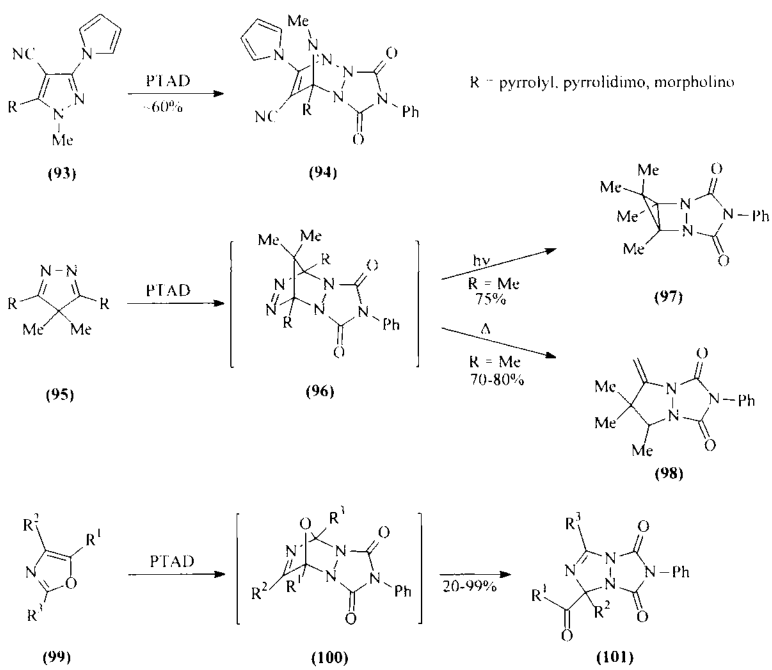
4. *Additions with Heterocyclic Dienes*

Diels–Alder addition of TADs, especially PTAD, to various five-, six-, and seven-membered heterocyclic systems has been described. For example, amino-substituted pyrazoles **93** give the corresponding [4+2] adducts

94 (88T7155; 89CZ181). Isopyrazoles **95** react with PTAD as typical diazadienes to provide [4+2] addition products **96.** Photochemical (68JA5330; 70JA6218; 95JOC308) and thermal (68JA5330; 70JA6218) extrusion of dinitrogen led to housanes **97** and pyrazolopyrazoles **98,** respectively. Similar isopyrazole *N*-oxides also add PTAD to give azoxy derivatives corresponding to **96** [72JCS(CC)867].

Oxazoles **99** react with PTAD to give bicyclic compounds **101,** which are products of rearrangement of the initial Diels–Alder adducts **100** (84-LA641; 88CL1551; 89T3535; 92BCJ2998). Similar reaction of 5-alkoxythiazoles has also been described (92BCJ3315). However, for R^1 = MeO, R^2 = 4-nitrophenyl, and R^3 = Me, the corresponding adduct **100** is reported by other authors to be the final product of the reaction (86BCJ433).

2,6-Dimethoxythiophene (**102**) treated with PTAD in methanol affords a high yield of **103,** a product of the Diels–Alder reaction and subsequent solvolysis with methanol [82JCS(CC)1033]. Reaction of thiophene dioxides **104** bearing bulky substituents at positions 3 and 4 with excess of PTAD gives good yields of **105,** products of bis addition and extrusion of sulfur dioxide. Treatment of these adducts with potassium hydroxide at room



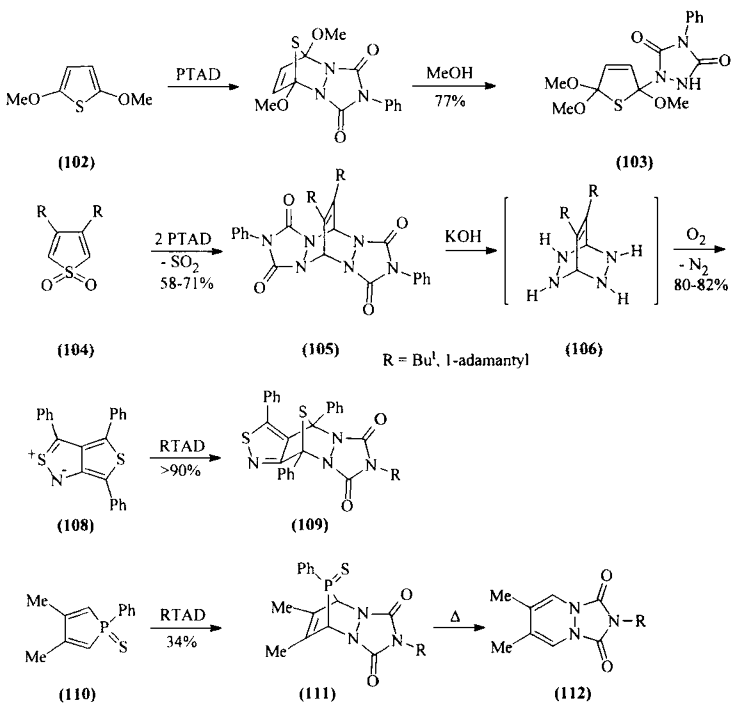
SCHEME 18

temperature gives goods yields of **107,** products of subsequent air oxidation and nitrogen extrusion. Expected intermediate **106** cannot be isolated even when the reaction is carried out under an inert atmosphere because of its easy oxidation during workup [89H(29)1241; 90JA5654, 90JA7648].

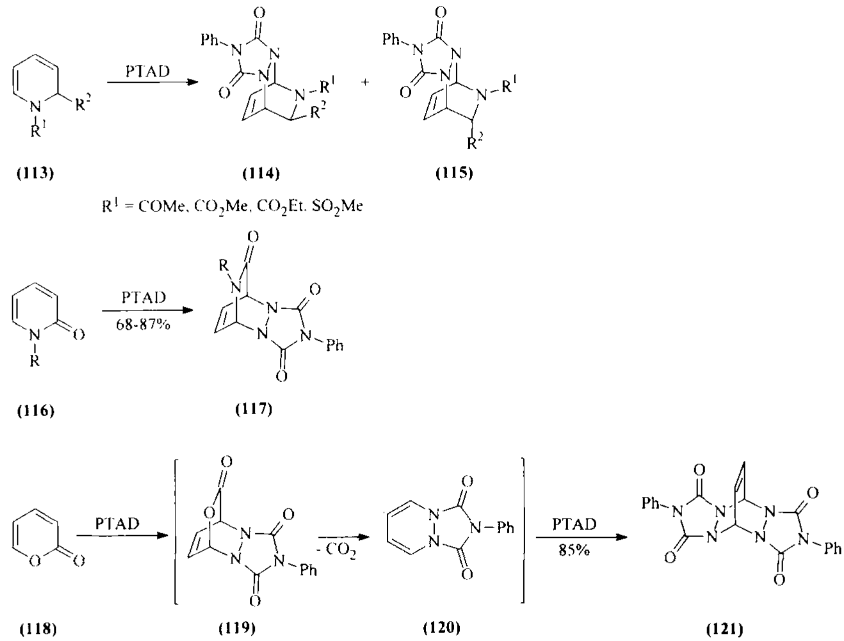
Thieno[3,4-*c*]isothiazole **108** reacts with PTAD or MTAD to give the corresponding [4+2] adducts **109** (86LA1796). The similar thieno[3,4-*f*][2,1]benzisothiazole derivative gives an analogous product (86CB3158).

Thioxophosphole **110** undergoes Diels–Alder type reaction with TADs to adducts **111;** their thermolysis in toluene then provides [4+1] cycloreversion products **112.** The same reactivity has also been observed for similar selenoxophospholes (Scheme 19) [85PS(25)201].

Several 1,2-dihydropyridine derivatives **113** have been successfully used as dienes in the Diels–Alder trapping by TADs to give the corresponding products (Scheme 20). *N*-Acetyl derivatives give a mixture of both exo and endo isomers **114** and **115,** respectively, whereas *N*-alkoxycarbonyl and



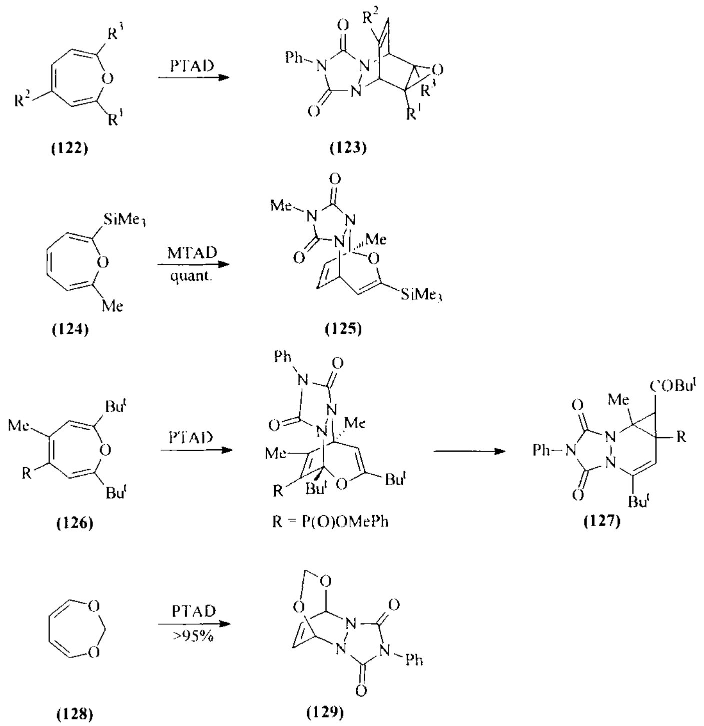
SCHEME 19



SCHEME 20

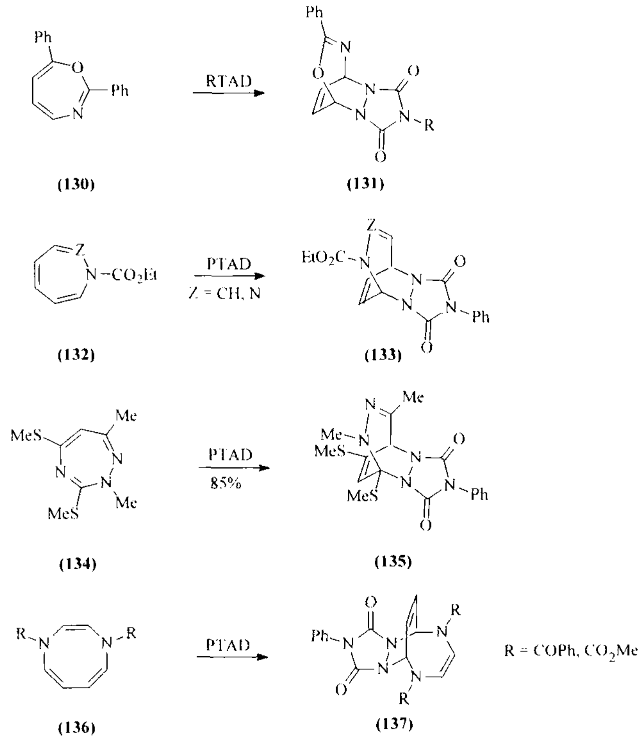
alkanesulfonyl derivatives give exclusively the exo isomers **114** (74JHC843; 76JHC481). *N*-Alkyl-2-pyridones (**116**) have been shown to give the corresponding 1,4-adducts **117** in good yields (76JHC673, 76ZOR2270; 78ZOR841). Similar cycloadduct **119**, formed from 2-pyrone (**118**) and PTAD, extrudes carbon dioxide to give **120**, which reacts with additional PTAD to give an 85% yield of the final product **121** (76ZOR2270). 3-Methoxycarbonyl-2-pyrone provides with PTAD exclusively the corresponding 1:1 adduct analogous to **120** (84JOC587).

Oxepin derivatives **122** react with PTAD to form adducts **123**, which are derived from their valence tautomeric benzene oxides (79JOC468; 87JOC3851). However, some oxepins react in a different way, as it is shown by the reaction of **124**, which leads to **125** (79JOC468). Treatment of several oxepin derivatives **126** with PTAD resulted in [4+2] cycloaddition, followed by hetero-Cope rearrangement to give **127** as the final products (85CB3700). 1,3-Dioxepin (**128**), which is unreactive toward *N*-phenylmaleinimide or *p*-benzoquinone, reacts with PTAD at room temperature to give a nearly quantitative yield of the corresponding [4+2] adduct **129** (76TL2113).



SCHEME 21

1,3-Oxazepine **130** with MTAD or PTAD gives typical Diels–Alder products **131** [78H(11)331]. Similarly, azepine (Z = CH) and 1,2-diazepine (Z = N) derivatives **132** add PTAD to give high yields of the corresponding [4+2] adducts **133** [70JCS(CC)82; 71JCS(C)2142; 74T2851]. Similar 2,3-dihydro-1,2(1*H*)-diazepines treated with PTAD give the expected Diels–Alder products (75CJC519). 1,2,4-Triazepine derivative **134** gives with PTAD the corresponding [4+2] adduct **135,** whereas reaction of this heterocyclic system with dienophiles such as maleic anhydride or dimethyl acetylendicarboxylate affords products of [1,3]sigmatropic rearrangement (85JHC25). 1,4-Disubstituted diazocines (**136**) treated with PTAD give Diels–Alder adducts **137** (80CB3161).

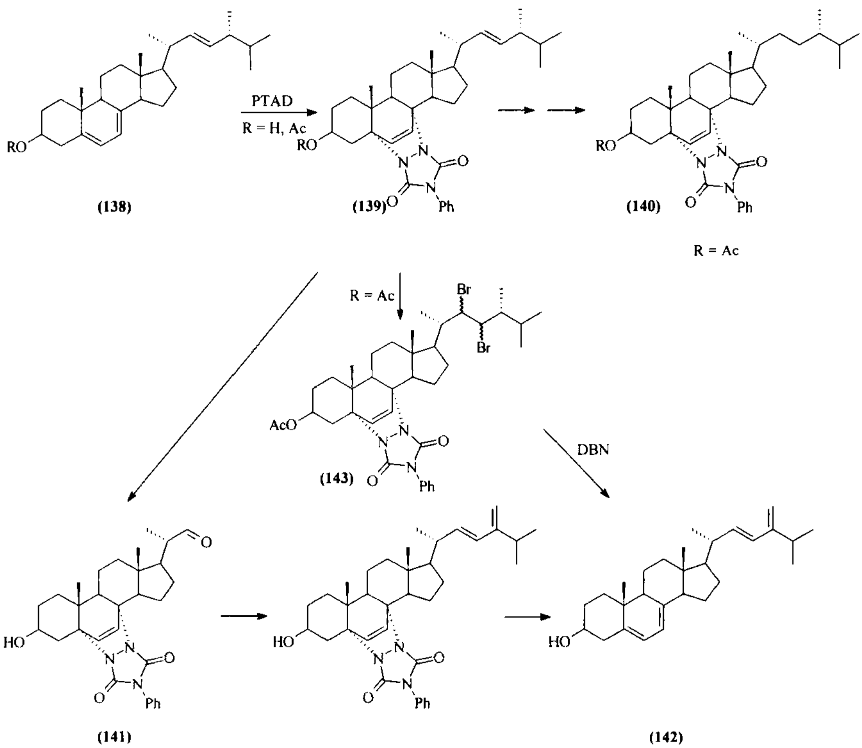


SCHEME 22

5. *Use of Diels–Alder Addition for Protecting a 1,3-Diene System*

Protection of a diene system by cycloaddition with suitable dienophiles is an attractive method for specific structural modifications. The use of TADs is advantageous for their high reactivity and their stability as adducts under various reaction conditions. The range of dienes that can be protected is somewhat limited to compounds having substituents compatible with the reaction conditions. The reactivity of double bonds situated in a urazole-moiety-containing molecule toward electrophiles may be entirely suppressed or retarded depending on their distance from the electron-withdrawing urazole moiety [78H(11)359]. This effect can be exploited for selective suppression of electrophilic attack, e.g., in steroid chemistry.

a. *Protection of Steroids.* Adducts of steroidal 5,7-dienes with TADs are often used for protection (Scheme 23). Synthetic manipulations of ergosterol (**138**) (R = H) and its derivatives, e.g., acetate (R = Ac), other than at the 5,7-diene system require an efficient method of protection. Reaction with PTAD provides adducts **139** in good yields and the adducts can be easily deprotected by LAH [70JCS(CC)939; 71JCS(C)1968], potassium carbonate in DMSO or DMF at 120°C [78JCS(CC)727; 79JCS(P1)1858], heating with organic bases (tetramethylguanidine or 2,4,6-trimethylpyridine) [79JCS(CC)164], or preferentially by DIBAL [95JCS(P1)2679]. Simple and reversible protection of the diene system can be achieved [66JOC2397; 70JCS(CC)939; 71JCS(C)1968; 76JCS(P1)821, 76JCS(P1)826; 81JOC3422; 87ZOB2529]. Catalytic hydrogenation of these adducts shows a preference for 6,7 attack, but electrophilic attack on this system generally occurs selectively at the 22,23 double bond. An interesting application involves a sequence leading to **140** [76JCS(P1)821]. Similarly, selective epoxidation of this double bond with MCPBA can be achieved,

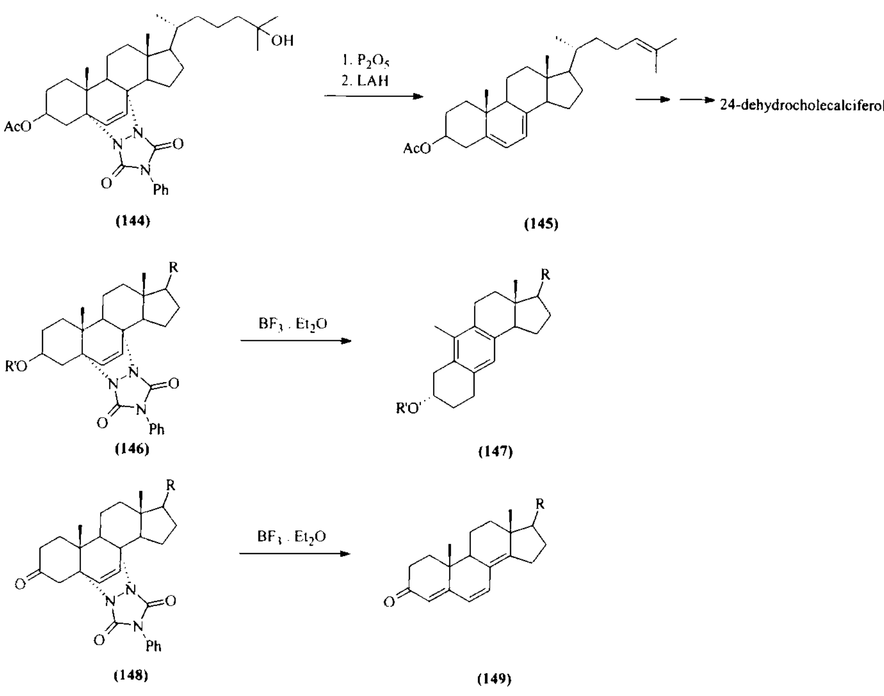


SCHEME 23

and the epoxy ring is not cleaved with LAH under conditions used for the deprotection of the steroid (87ZOB2529). The same type of protection has been used for the synthesis of tetraene **142** via aldehyde **141** [70JCS(CC)-939; 77JCS(P1)809] or via the dibromo derivative of acetoxy derivative **143**, which, treated with DBN, gives **142** directly [77JCS(P1)809]. Similar manipulations have been described for many other steroids (74T2701; 81MI1, 81TL2591; 84B1983, 84CPB1416; 89BCJ2599, 89BCJ3132; 92JOC33, 92TL3741).

Urazole **144** dehydrated by phosphorus pentoxide and deprotected by LAH gives cholestadienol **145**, which after irradiation and isomerization provides 24-dehydrocholecalciferol (80MI1). When adducts **146** are treated with BF_3 etherate, oxidative rearrangement gives anthrasteroids **147** in high yields [77JCS(P1)805]. Similar adducts of steroidal 5,7-dien-3-ones **148** treated with BF_3 etherate provide 4,6,8(14)-triene-3-ones **149** [75JCS-(CC)633; 77JCS(P1)820].

Steroidal 3-keto-4,4-dimethyl-5,7-dienes **150** also form 1 : 1 adducts with PTAD, but these adducts have been identified as the ene reaction products



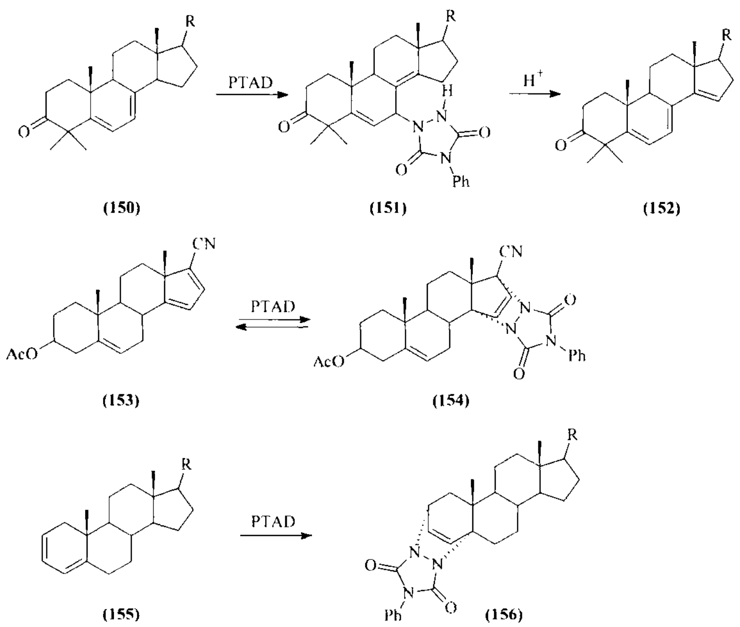
SCHEME 24

151. These urazoles are decomposed by acidic reagents to give 5,7,14-triene-3-ones **152** [75JCS(CC)633; 77JCS(P1)812].

PTAD also rapidly reacts with 3β-acetoxy-17-cyano-5,14,16-androstatriene (**153**) to give adduct **154.** However, this adduct rapidly decomposes to the starting material (65JOC769). Similar reaction with 16-methylpregna-4,14,16-triene-3,20-dione has also been described [68JCS(CC)1434]. $\Delta^{2,4}$-Cholestadiene (**155**) can also be protected by Diels–Alder reaction with PTAD, which gives **156** (66JOC2397).

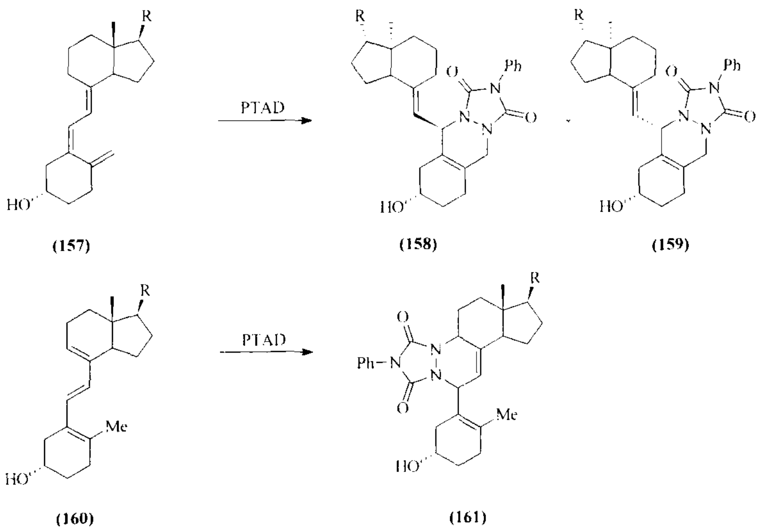
b. *Protection of Vitamin D Derivatives.* Since PTAD is widely used in steroid chemistry, its use in the protection of the vitamin D_3 diene system has also been studied. Vitamin D_3 (**157**) itself gives a mixture of products of Diels–Alder addition to the 5,10(19) diene of the 9,10-secocholestane system. Isomers 6α **158** (95%) and 6β **159** (5%) are formed. No addition to the 5,7-diene system is observed (76JOC2098). Provitamin D_3 (**160**) gives exclusively an adduct to the 6,8-diene system **161** (91T9419).

This type of protection has been used for many transformations of vitamin D_3 derivatives and/or precursors (75JCS(CC)633; 76JOC2098; 78LA745; 80HCA860; 82M427, 82TL995; 85T141; 91T9419]. Unfortunately, facile deprotection with LAH used in steroid chemistry is not effective in vitamin



(150) (151) (152) (153) (154) (155) (156)

SCHEME 25



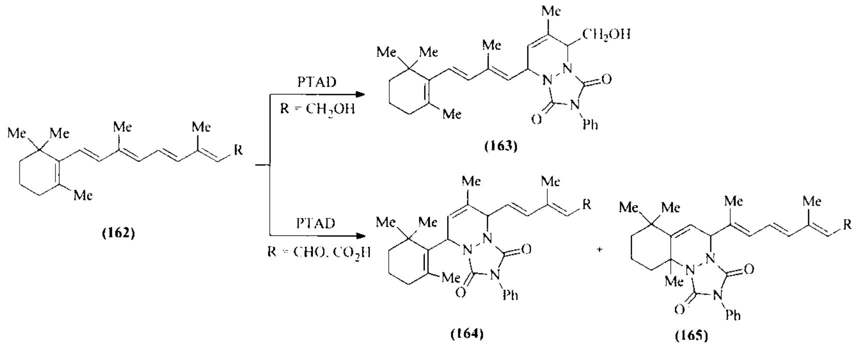
SCHEME 26

D_3 analogues (76JOC2098), and other, less efficient conditions are used, such as saponification by alkaline hydroxides in butanol or ethylene glycol.

6. *Use of Diels–Alder Addition for Isolation and Identification Purposes*

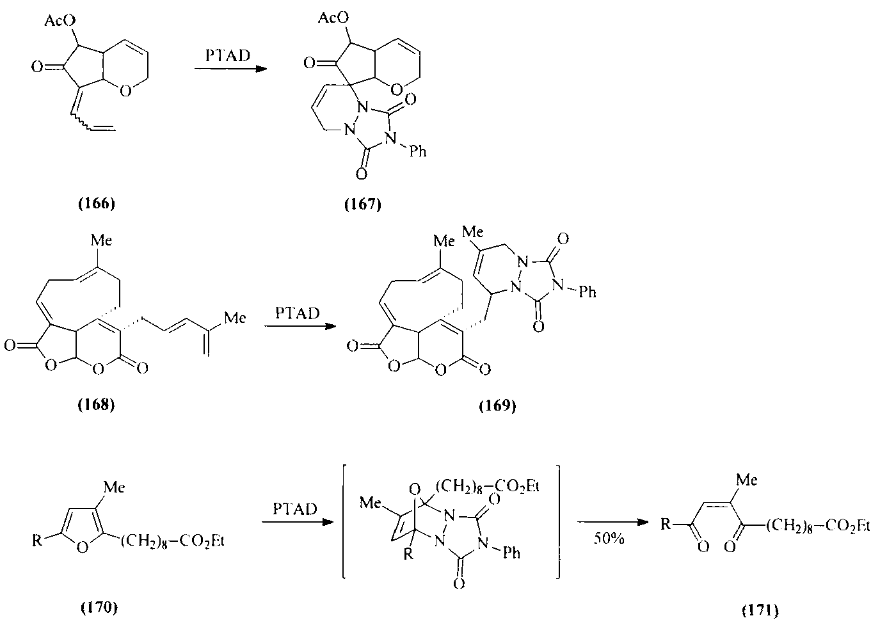
Adducts of PTAD with some steroidal 5,7-diene intermediates have been used for the isolation of these dienes from complex mixtures and, combined with deprotection with LAH, also for their purification (82CPB4593; 92CPB648). Similarly, PTAD adducts have been made with vitamin D analogues (76JOC2098; 92M439; 84M1453). The X-ray structures of these adducts have been used to determine the structure of the parent dienes (82M439; 84M1453).

A similar approach has also been used for the isolation of complex natural compounds. For example, vitamin A and its metabolites of a general formula **162** reacted with PTAD to give adducts with high regioselectivity depending on the nature of the terminal functional group R (Scheme 27). Retinol (R = CH_2OH) gave high yield of the 11,14 adduct **163,** together with a small amount of a bis adduct. Retinal (R = CHO) or retinoic acid (R = CO_2H) gave high yields of the 7,10 adduct **164,** together with a small amount of the 5,8 adduct **165** (83JA4829; 91TL2379).



SCHEME 27

There are many other cases in which TADs, especially PTAD, have been used for isolation and identification of complex natural compounds. The following several examples demonstrate several possible strategies (Scheme 28). Two metabolites isolated from marine sponge *Ulosa* spp. have been acetylated to acetates **166** and then isolated as their PTAD adduct **167.** Formation of a single adduct from both acetates confirmed that the metabolites were geometrical isomers about the exocyclic double bond (78TL961).

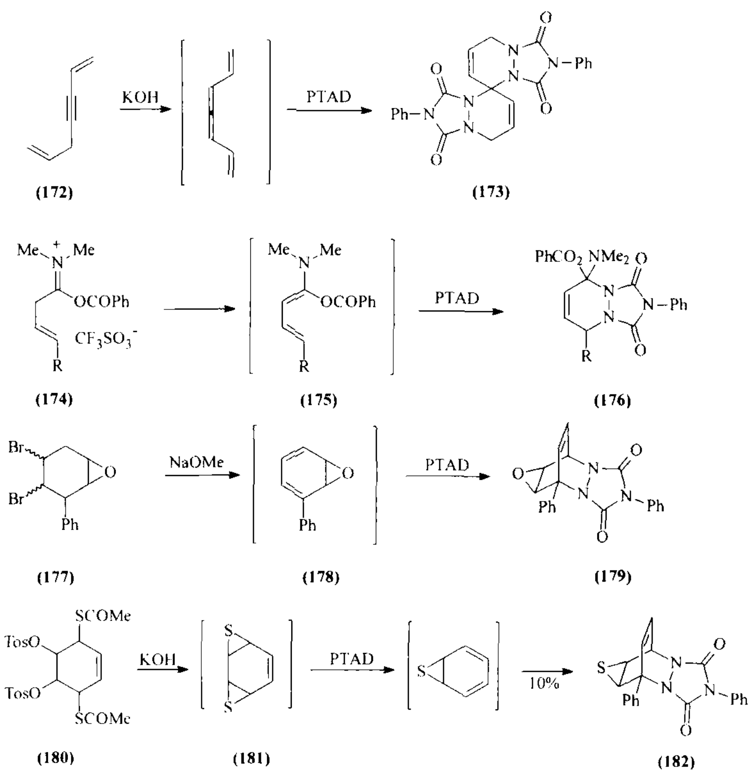


SCHEME 28

Diterpene **168** and several similar compounds were isolated from brown alga *Dictyota prolificans.* The presence of the 1,3-diene in **168** was secured by its rapid reaction with PTAD and the mass spectrum of the adduct **169** proved the structure (82AJC121).

The substitution pattern in two homologous furans isolated from brown alga *Acrocarpia paniculata* was determined by their reaction with PTAD. Compound **170,** provided diketone **171** as the final product formed via the corresponding Diels–Alder adduct. Structure elucidation of this product then proved the structure of **170** (82AJC165).

Identification of some unstable natural products has been based on the identification of their adducts with PTAD (82P739; 83JA4829; 91HCA-2035). The same method has also been used for the identification of some unstable intermediates. For example, unstable 1,3,6,6-heptatetraene (divinylallene), which is formed by treatment of **172** with potassium hydroxide, can be trapped by excess PTAD to give spiro compound **173** (75AG492).



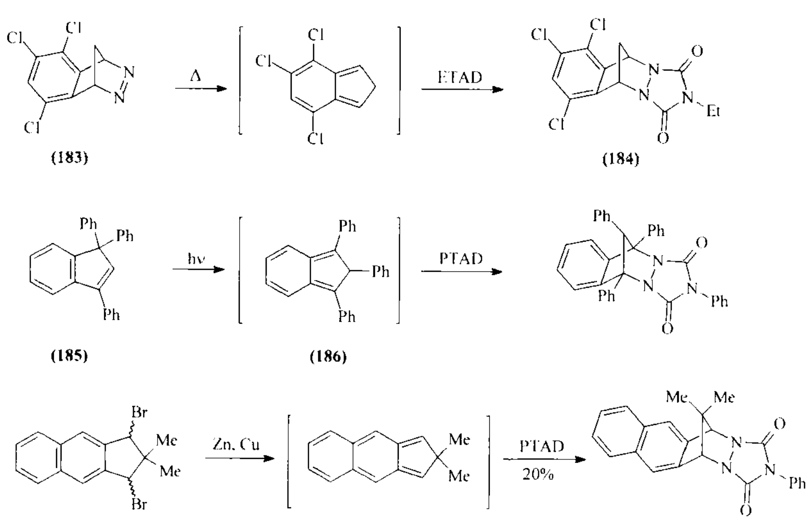
SCHEME 29

Imminium triflates **174** are readily deprotonated with triethylamine or pyridine to give unstable 1-acyloxyenamines **175,** which, in the presence of PTAD, are trapped to give Diels–Alder adduct **176** [80JCS(CC)790].

Unstable benzene oxides (78JOC2711) and sulfides (74AG818) have also been identified as the corresponding PTAD adducts. Compound **178,** an example of the former derivatives, is formed by dehydrohalogenation of **177** with sodium methoxide. Similarly, thermally unstable bis-episulfide **181** is formed from ditosylate **180.** When either **178** or **181** was treated with PTAD, the corresponding adducts **179** and **182** were obtained in reasonable yields.

Trapping with TADs has also been used to prove the structure of isoindene intermediates. Azo compound **183** is thermally decomposed in the presence of ethyl-TAD to give **184** via the corresponding retro Diels–Alder product (70TL3241). Irradiation of 1,1,3-triphenylindene (**185**) in cyclopentane gives a solution containing 1,2,3-triphenylisoindene (**186**), which has been trapped with PTAD (77JA8257). Isoindene derivative **188,** formed by dehalogenation of a dibromo precursor **187,** has also been trapped with PTAD (82JOC2298).

Unstable trimethylene cyclopentane **190,** generated *in situ* from **189** by a Wittig reaction, was trapped with PTAD to give a 25% yield of the (*E*) isomer **191** (88CB2127). *cis*-Methoxystyrene easily reacts with singlet



(183) (184) (185) (186) (187) (188)

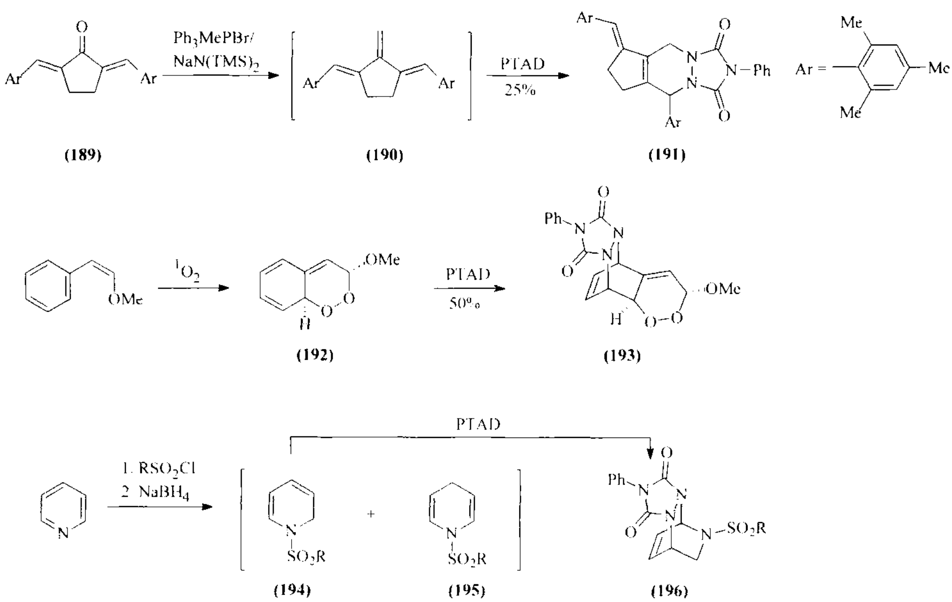
SCHEME 30

oxygen to provide unstable compound **192,** which can be trapped with PTAD to give good yield of **193** (78TL3227).

Reaction of alkylsulfonyl or arylsulfonyl chlorides with pyridine in the presence of sodium borohydride afforded *N*-sulfonyl-1,2- and 1,4-dihydropyridines **194** and **195,** respectively (77CJC1788). Separation of this mixture by conventional methods failed, but when the mixture was treated with PTAD, **194** provided its Diels–Alder adduct **196,** and then pure 1,4-dihydro derivative **195** was easily obtained by chromatography.

Unstable and hitherto unknown 2-azanorbornadiene has been generated, and its presence has been characterized spectroscopically. Its instability is due to a retro Diels–Alder reaction leading to cyclopentadiene and hydrogen cyanide. Addition of PTAD accelerated the retro reaction, and instantaneous quantitative formation of the Diels–Alder adduct of cyclopentadiene and PTAD proved the process (91TL6957).

The following unusual example should be applicable in many similar cases. Preparations of a silica-gel-supported TAD derivative has been developed, and this immobilized agent was used for the separation of several mixtures of natural compounds (83JOC2654). For example, ergosterol can be effectively separated from cholesterol. This silica-gel-supported TAD was also used to remove the phase transfer catalyst *N*-(*E,E*)-8,10-

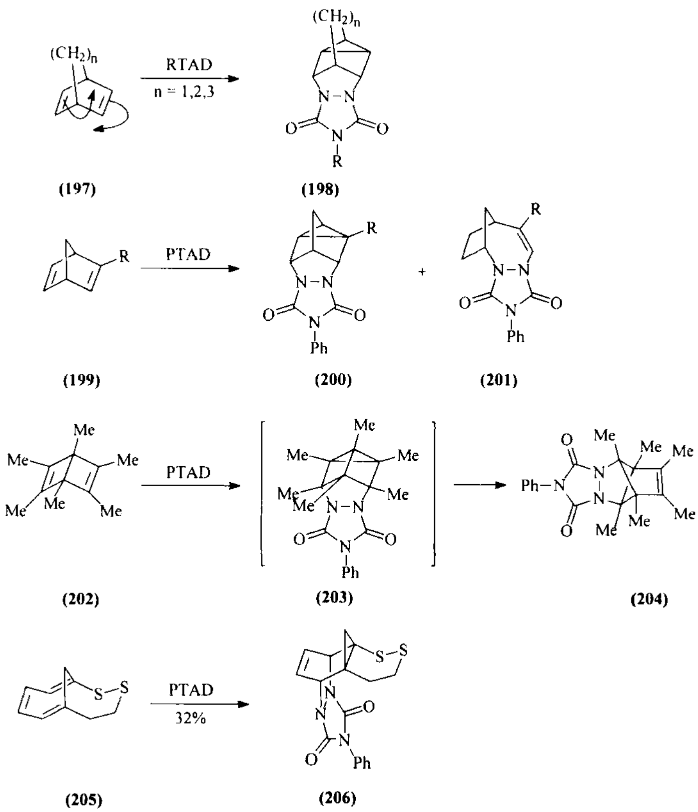


SCHEME 31

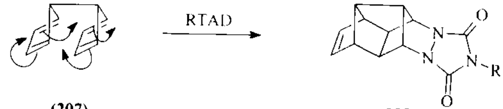
dodecadien-1-yl]trimethylammonium mesylate from reaction mixtures (83SC729).

7. *Homo and Domino Diels–Alder Reaction*

If the geometry of a diene is suitable, the diene component of the Diels–Alder reaction can even be nonconjugated. This is the case of homo Diels–Alder addition, a 1,5 addition of dienophiles to 1,4-dienes [67JOC330; 71JA1300; 80JCS(P1)2425; 85JA4554], shown in Scheme 32 where, when n = 1, 2, or 3, the structure **197** has a suitable geometry to give homo Diels–Alder adducts **198.** Some substituted derivatives **199** give mixtures of homo Diels–Alder adducts **200** and insertion products **201.** With increasing electron-withdrawing effect of the 2-substituent, the amount of the insertion product increases at the expense of the homo Diels–Alder product



SCHEME 32



(207) (208)

SCHEME 33

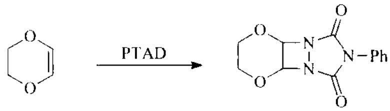
(87CB531). Dewar benzene **202** treated with PTAD gives compound **204.** Formation of this product can be explained by the intermediacy of the labile homo Diels–Alder adduct **203** (66JA5934). Similar 1,5 addition of PTAD to bicyclic disulfide **205** leading to **206** has also been described (84JA5271).

Dihydrofulvalene (**207**), generated *in situ* at −78°C by oxidative coupling of sodium cyclopentadienide with iodine, treated with PTAD gave a complex mixture from which a 3% yield of **208,** a product of domino Diels–Alder addition, was isolated (74TL2433; 78JA5845). In domino Diels–Alder addition, two diene systems are involved (Scheme 33). A significantly less reactive perchlorinated dihydrofulvalene derivative when heated with MTAD for 3 days afforded 63% of the corresponding domino adduct (78JA5845).

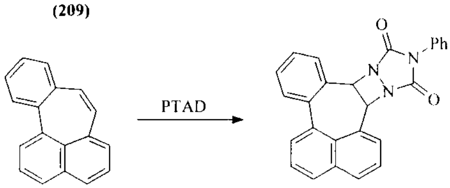
B. 1,2 ADDITION

Compounds containing isolated double bonds with no allylic hydrogen atom, which therefore cannot be involved in the ene reaction, usually react with TADs by a 1,2-cycloaddition. For example, dihydro-1,4-dioxane (**209**) (70JOC1155) or tetracyclic compound **210** (81JOC1931) give the corresponding 1,2-addition products (Scheme 34). Cyclobutadiene derivative **211** affords regioselectively Dewar benzene analogue **212** (82CB3796). Adamantylidene adamantane (**213**) treated with PTAD gives the corresponding [2 + 2] adduct **214** (80JA6384; 84JOC2910). Similar [2 + 2] addition of TADs to methylene adamantane has also been described (76T437). The adduct **214** at 70°C undergoes a cycloreversion reaction to give PTAD and starting adamantylidene adamantane. Therefore, the adduct can be used as a source of PTAD in reactions that require prolonged heating with PTAD, since PTAD itself is extensively degradated under such conditions. This reagent minimizes PTAD degradation, fewer by-products are usually formed, and nearly stoichiometric amounts of PTAD can be used (86S854).

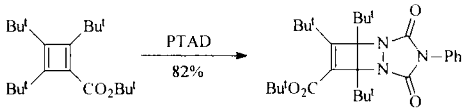
Some compounds having an allylic hydrogen atom react by [2 + 2] cycloaddition. Furan **215** (86AG1006), methylenecyclopropane **216** (72-TL2995; 74JA6944), vinylcyclopropane **217,** (73TL713), and some norbornene derivatives **218** (81TL929), shown in Scheme 35, are typical.



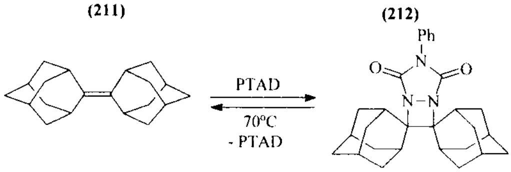
(209)



(210)

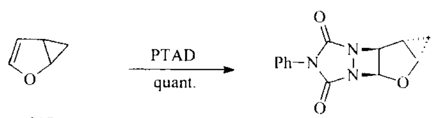


(211) **(212)**

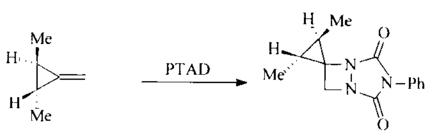


(213) **(214)**

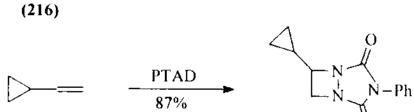
SCHEME 34



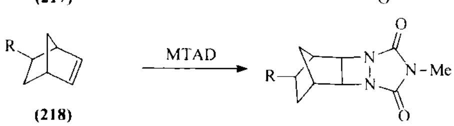
(215)



(216)

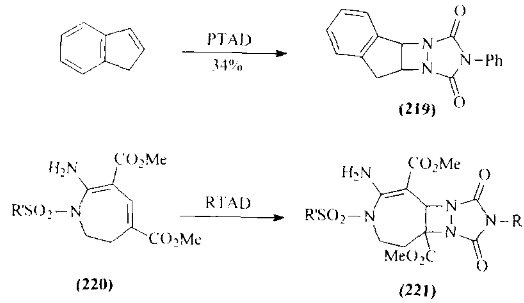


(217)



(218)

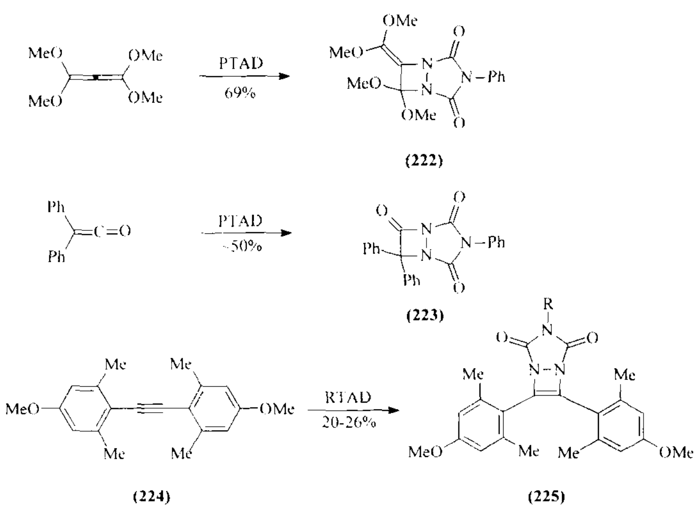
SCHEME 35



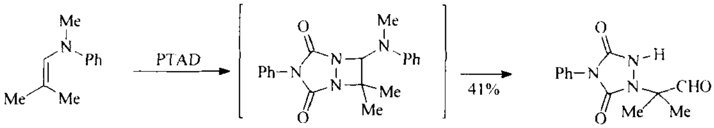
SCHEME 36

Indene derivatives (70JOC1155; 88TL2769) with TADs also form [2 + 2] adducts, e.g., **219.** Interestingly, some 6,7-dihydro-1*H*-azepines, e.g., **220,** which are formally able to form both Diels–Alder and ene-type adducts, when treated with TADs provided only [2 + 2] adducts **221** (86CB2114).

An unusual 1,2-cycloaddition of PTAD to tetramethoxyallene giving 69% of **222** has been described (72AG306). Addition of TADs to diphenylketene proceeds the same way, affording **223** (84JOC2498). The reaction of MTAD or PTAD with substituted diphenylacetylene **224** provided 20–26% (isolated yields) of **225,** a product of 1,2 addition to the acetylenic bond (84JOC2917). This finding is interesting because similar phenyl and 4-methoxyphenyl acetylene give bis-(azomethine imines) (see Section IV,F).



SCHEME 37



(226) (227) (228)

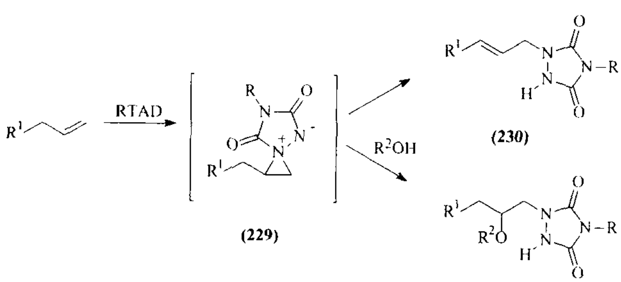
SCHEME 38

In some cases the first 1,2-adduct is further changed into a final product. For example, enamine **226** and PTAD give moderate yields of aldehyde **228** on forming the [2 + 2] intermediate **227** (74JHC787).

C. Ene Reaction

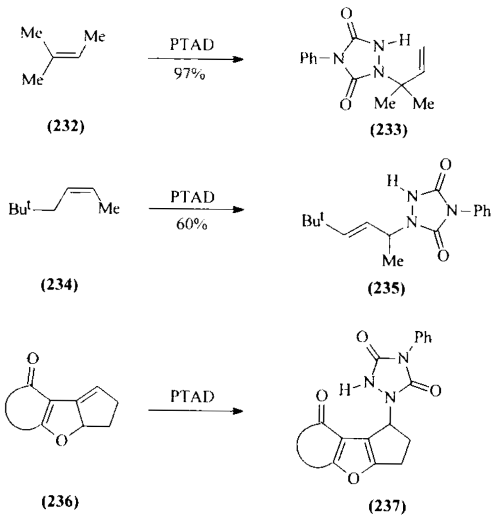
Reaction of TADs with electron-rich olefins possessing allylic hydrogen atoms in aprotic solvents often gives ene-type products (for a review, see 69AG597). The reaction proceeds with a shift of the allylic double bond from the α,β to the β, γ positions to give **230** (Scheme 39). Investigations using isotopes have concluded that an aziridinium imide intermediates **229** are involved (87TL15; 90JA3607, 90JA5364). The reaction is very sensitive to substituent effects, but the effects of solvent and TAD are usually small (80JOC3472). However, in alcoholic solutions, especially at lower temperatures, TADs provide alkoxy adducts **231** (91TL2667).

The ene reaction has been described for a wide variety of olefins, both acyclic and cyclic [67JCS(CC)760; 77JCS(P1)1463; 80JA6384, 80JOC3467; 84JOC2910]. The photochemical ene reaction of *trans*-cycloheptene with MTAD has been described to proceed via the corresponding aziridinium imide (90JA5364). Selected examples of the ene reaction are shown in Scheme 40. With unsymmetrical olefins, the reaction is sometimes surprisingly stereospecific, e.g., **232** gives only **233**. In *cis*-alkenes, a preferential abstraction of the allylic hydrogen on the side of the larger alkyl groups



(229) (230) (231)

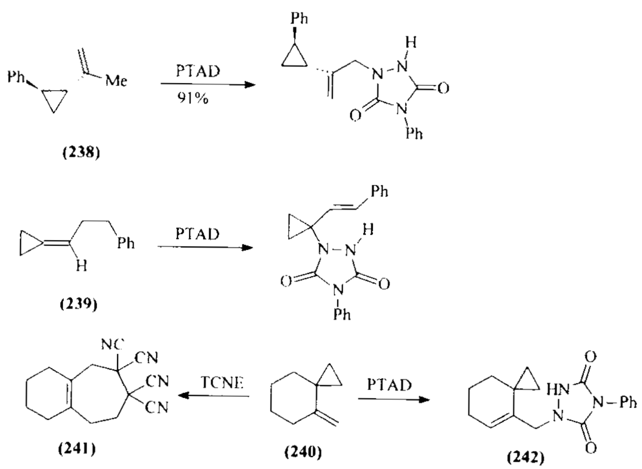
SCHEME 39



SCHEME 40

on the double bond has been observed (89TL6903; 90TL5775). For example, **234** treated with PTAD gave urazole **235.** Sometimes the allylic double bond is a part of a heterocyclic system, e.g., tricyclic furans of general formula **236** provided urazoles **237** with PTAD (88LA371).

In spite of the fact that exomethylenecyclopropanes or vinyl cyclopropane derivatives usually react by 1,2 addition, trans-2-phenyl-1-(2-isopropylidene)cyclopropane (**238**) as well as cyclopropylidene **239** give

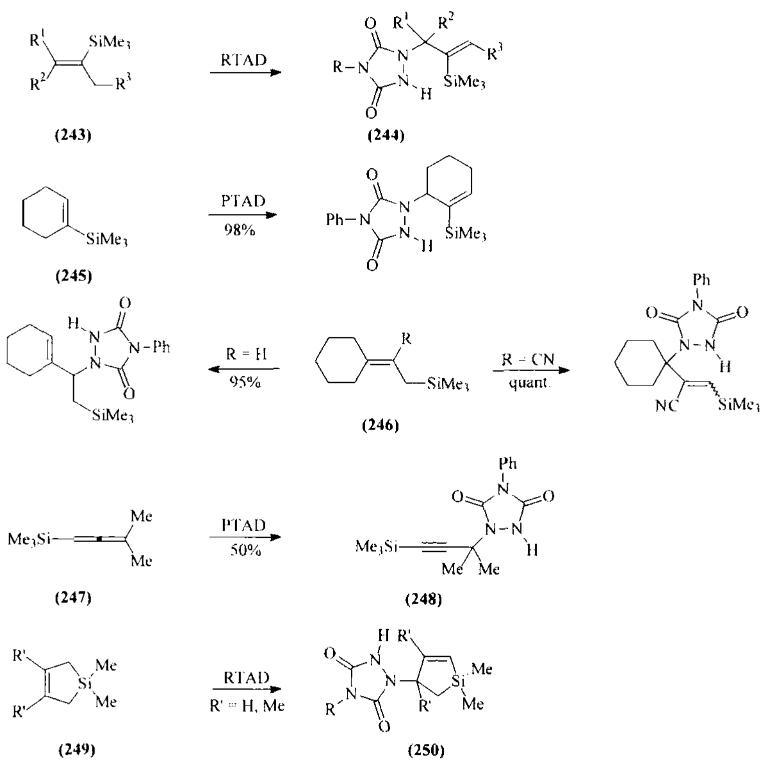


SCHEME 41

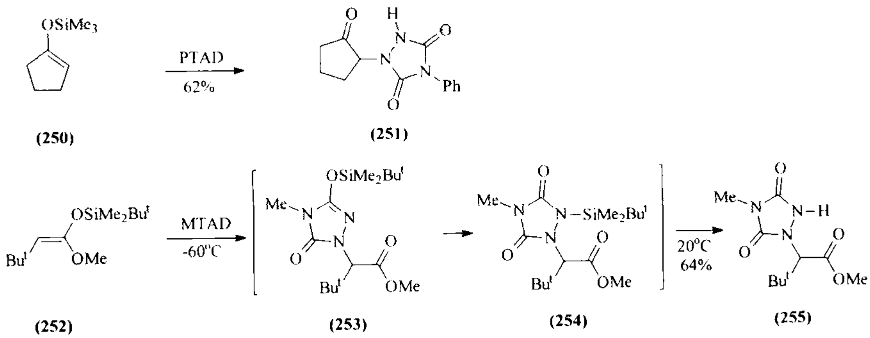
only the corresponding ene products (72TL2995). Spiro compound **240,** which with TCNE gives the unusual bicyclic product **241,** when treated with PTAD gives only the corresponding ene product **242** [73JCS(CC)859].

The ene reaction of TADs with vinylsilanes **243** proceeds with hydrogen abstraction from the position geminal to the silyl group with formation of **244.** The same is true also for cyclic compound **245** [81JOC614; 85JOM(281)149; 92CB243]. But for compounds of a general formula **246** possessing an exocyclic double bond, the course of the reaction is strongly dependent on the character of the R substituent [79JCS(CC)548]. Allylsilane **247** treated with PTAD gives propyne derivative **248** (78T2669). Ene reaction of silacyclopentenes **249** with TADs leading to the corresponding ene products has also been described [75CR(C)787; 78T2669].

PTAD reacts with silyl enol ether **250** to give **251,** which can be considered as an ene-type product (85SC649). In the case of ester **252,** low-temperature NMR experiments revealed that labile ene product **253** was initially formed



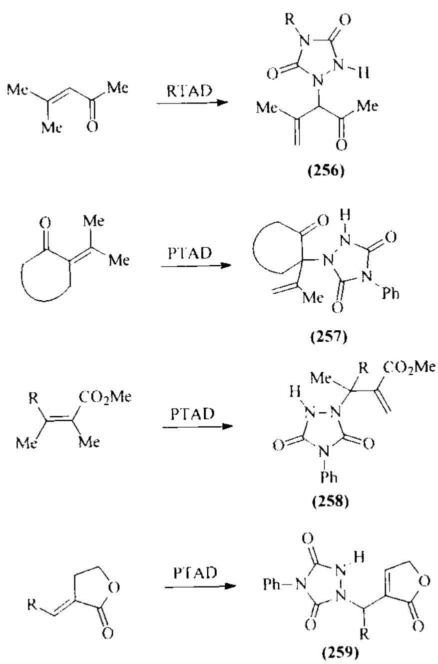
SCHEME 42



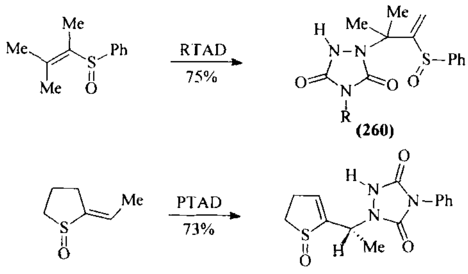
SCHEME 43

and a subsequent silyl group migration led to **254.** After workup, urazole **255** was then isolated (91JOC7244).

TADs easily react with α,β-unsaturated ketones (76TL3773; 82CJC835), esters (92JA6044), and lactones (80JOC4287; 81JOC1198; 92JA6044) to give the corresponding ene products **256, 257, 258,** and **259,** respectively (Scheme 44).



SCHEME 44

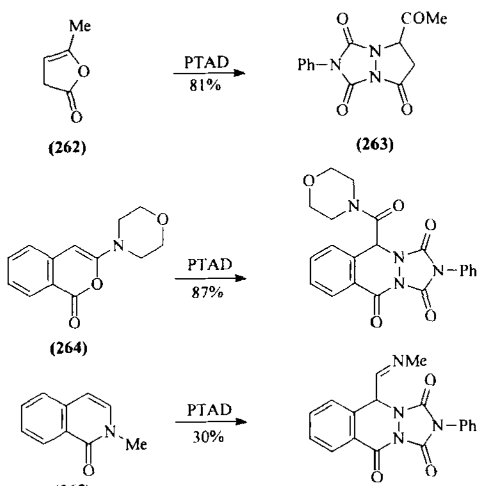

(260)
(261)

SCHEME 45

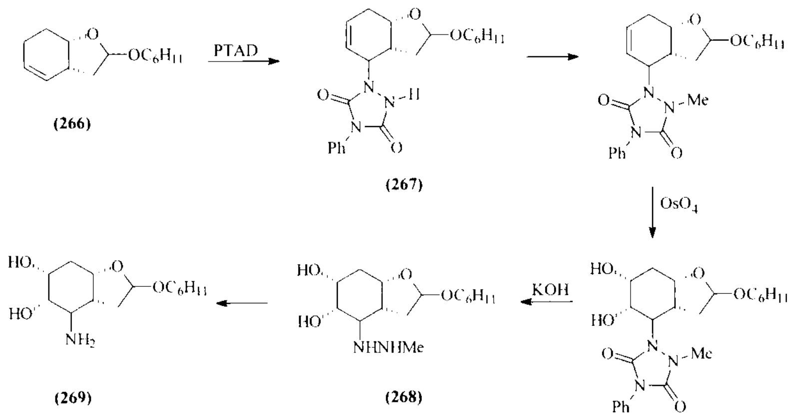
Similarly, α,β-unsaturated sulfoxides provide the corresponding ene products, e.g., **260** and **261** (Scheme 45) (89T6657; 90TL5775).

5-Methylfuran-2(3*H*)-one (α-angelica lactone) (**262**) reacts with PTAD by an ene-type reaction involving acyl group transfer to yield bicyclic structure **263** [80JCS(P1)843]. Similar acyl transfer has also been observed in the reaction of PTAD with 3-morpholinoisocoumarin (**264**) [76JCS(CC)650; 78JCS(P1)1351] and 2-methylisoquinolin-1-one (**265**) [80JCS(P1)843] (Scheme 46).

A well-known application of the ene-type reaction is that used by Corey in the synthesis of amine **269**, an important intermediate leading to PGF2 and PGE2 (Scheme 47). Starting enol **266** when treated with PTAD gave


(262) (263)
(264)
(265)

SCHEME 46



SCHEME 47

the ene-type product **267**. Hydroxylation of its double bond was not possible directly, but could be effected in good yield after methylation of the acidic urazole hydrogen. After hydroxylation, the urazole was hydrolyzed to hydrazine **268,** which was then transformed into the required amine (73TL3091). A similar method of shifting double bond in ring D of steroids to the corresponding exocyclic position has also been described (75JA-6580; 77JA905).

D. Cycloaddition Reactions Involving Cyclopropane Strained σ Bonds

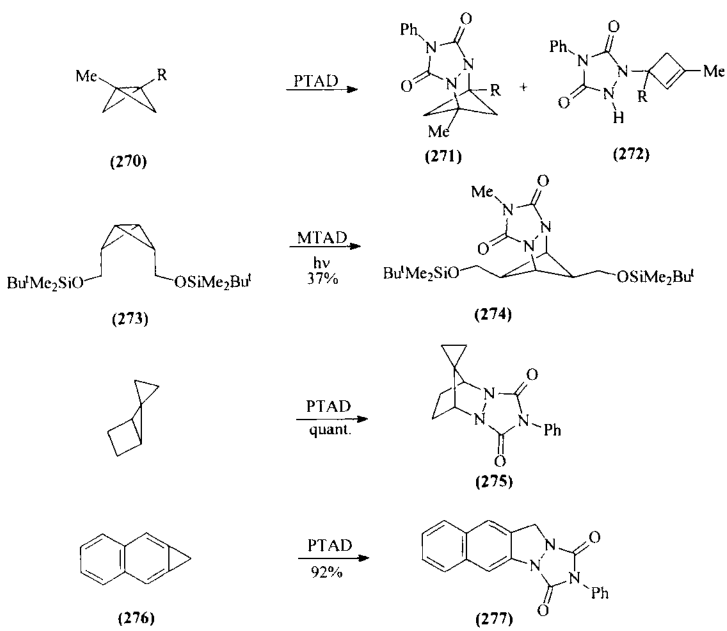
Several examples of participation of the strained σ bonds in cyclopropane in [2 + 2] cycloaddition reactions with TADs have been described. Ordinarily, cyclopropanes do not undergo the reaction, but addition has been accomplished with strained systems such as bicyclo[1.1.0]butanes and bicyclo[2.1.0]pentanes. For example, bicyclobutane **270** reacts with TADs to give a mixture of [2 + 2] addition product **271** and ene-reaction product **272.** The product ratio is highly dependent on the bicyclobutane substituent R. When a more electron-withdrawing substituent is present, more [2 + 2] addition occurs. For example, the dimethyl derivative (R = Me) gives only the corresponding ene reaction product **272,** whereas the cyano derivative (R = CN) yields exclusively the corresponding [2 + 2] cycloaddition product **271** (81JOC4090; 84JA4211). Treatment of parent bicyclo-[1.1.0]butane with TADs in various solvents gave complex mixtures. Interestingly, the addition of TADs to a solution of bicyclo[1.1.0]butane in a

large volume of hexane at 63°C is reported to give only the [2 + 2] addition product (81JOC4092). Thermally unreactive, endo,endo-derivative **273** reacts with MTAD under photochemical conditions to give a 37% yield of **274** (89JA3927).

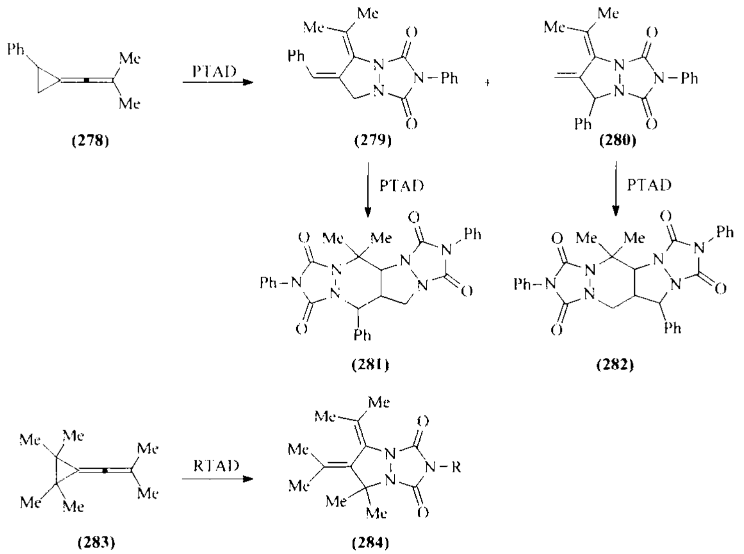
As in bicyclo[1.1.0]butanes, bicyclo[2.1.0]pentanes react with TADs to give the corresponding [2 + 2] products, e.g., **275** (67TL4695; 84JA3466, 84JA4211).

Cyclopropa[*b*]naphthalene (**276**) with PTAD reacts quickly to open the three-membered ring to give **277** in almost quantitative yield (90AJC2099).

Examples of participation of cyclopropane's strained bonds in [4 + 2] cycloaddition reactions with TADs are rare. In fact, the only [4 + 2] cycloaddition of this type is a reaction of allenylcyclopropanes, e.g., **278,** with PTAD, which affords a mixture of adducts **279** and **280** together with a small amount of a 2:1 adduct **282** (71JA2562; 73JA1553; 74JA6220, 74JA6944, 74TL1933). The reaction occurs in a fully concerted manner involving an eight-electron transition state in which both allene double bonds are involved. Both 1:1 adducts **279** and **280** are able to react with additional



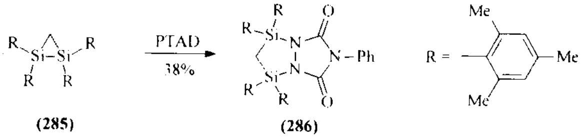
SCHEME 48



SCHEME 49

PTAD to give **281** and **282,** respectively. Since **280** reacts with PTAD at least 100 times faster than **279,** no **281** is found. Reaction of **283** with TADs provide only 1 : 1 addition product **284** (73JA1553). The structure was confirmed by X-ray spectroscopy for the 4-bromophenyl derivative (74JA6944).

Disilane **285** with PTAD has been shown to provide **286,** a product of urazole insertion into the strained silicon–silicon σ bond (91JA6286).



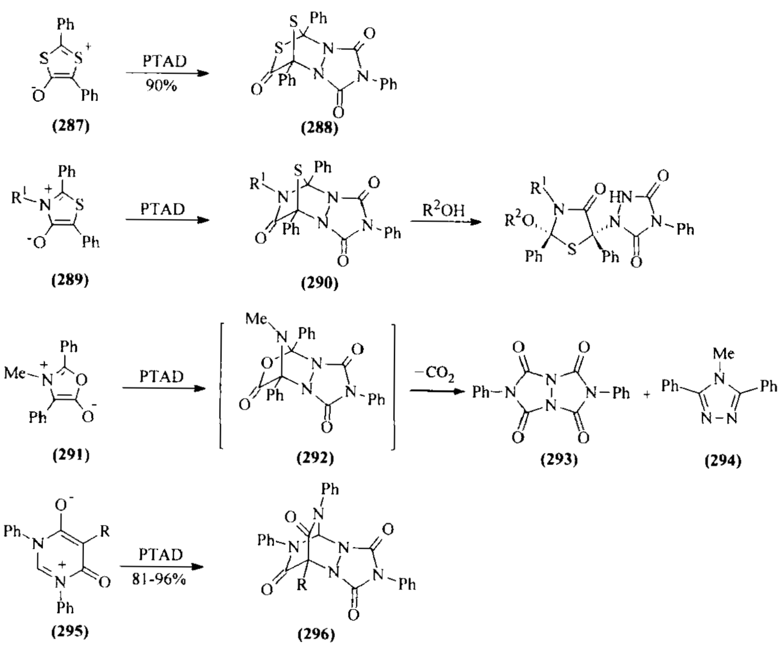
SCHEME 50

E. Reaction with Dipoles and Mesomeric Betaines

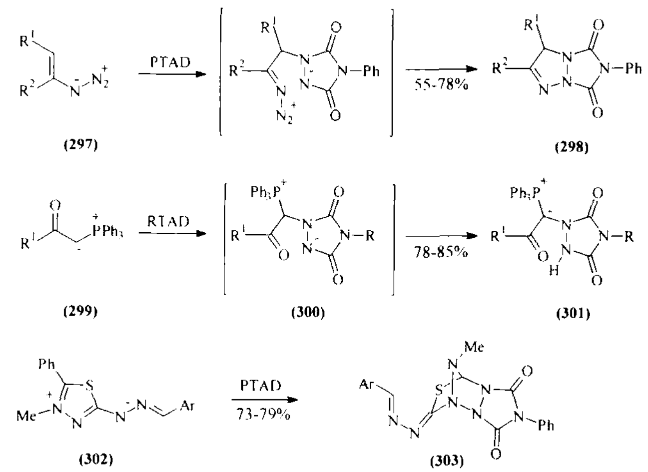
Mesoionic compounds **287** (78CB3171) and **289** [87JCS(P1)1979] add PTAD as 1,3 dipoles to give the corresponding products **288** and **290,** respectively. Compounds **290** react easily with water or alcohols to give the corresponding triazolidin-4-ones (Scheme 51). Mesoionic oxazoles **291** when treated with PTAD gave a 60% yield of bis-triazolidinone **293** and a 30% yield of triazole **294,** which presumably was formed via intermediate **292** (71CB1562).

5-Substituted (R = Ph, Me, $PhCH_2$) 3,6-dihydro-6-oxo-1-pyrimidinium-4-olates (**295**) treated with TADs provide products of 1,4-dipolar cycloaddition (**296**) (Scheme 51). In contrast, 5-unsubstituted derivative **295** (R = H) undergoes nucleophilic substitution to give the corresponding urazole (85CB4567).

PTAD reacts readily at room temperature with vinyl azides (**297**) to give **298,** 1,3-dipolar cycloaddition products of an intermediate vinyl nitrenes with PTAD. No addition of the azide 1,3-dipolar system to the N=N bond has been observed (76JOC2102). Ylides **299** treated with TADs initially



Scheme 51



SCHEME 52

provide dipolar intermediates **300**, which undergo intramolecular proton transfer to **301** (76JOC2102).

Masked azomethine imines **302** react nearly instantaneously with PTAD, but not with other reactive dipolarophiles, to give tricyclic products **303** [76JCS(CC)439; 79JCS(P1)724].

F. REACTIONS VIA DIPOLAR INTERMEDIATES

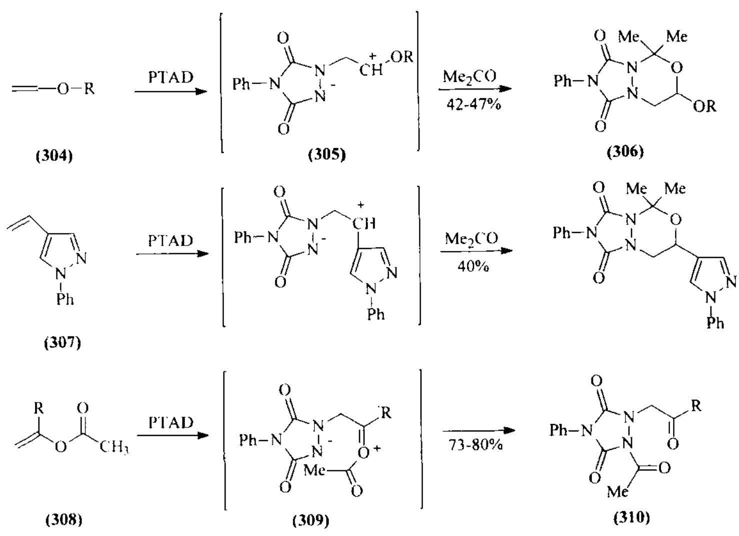
In some cases, products of reactions of TADs are best explained by the existence of 1,4-dipolar intermediates, and sometimes such intermediates have been observed. Some examples of [2 + 2] cycloaddition and ene reactions have been treated with the respective Sections IV,B and IV,C. There are many other types of reactions where such intermediates have been suggested and/or proved. For example, vinylethers **304** give with PTAD mixtures of 1,2-addition and polymeric products, the formation of which can be easily explained by 1,4-dipolar intermediates **305** (72JOC1454). In the presence of alkyl ketones, e.g., acetone, PTAD reacts spontaneously with vinyl ethers via these 1,4-dipoles **305**, which are able to add to weakly dipolarophilic acetone to form **306**, together with a polymeric material (71JOC2838; 83JOC822). A similar reaction takes place when 1-phenyl-4-vinylpyrazole (**307**) is treated with PTAD at −60°C in acetone (85TL6357).

Vinyl esters (**308**) give with PTAD dipolar intermediates **309**, which then undergo intramolecular nucleophilic attack by nitrogen on the carbonyl group, leading to the final products **310** [72JOC1454; 73JOC-3070; 78JCS(P1)1351]. The same reaction is observed for unstable 1-acyloxyenamines **308** where R = Me_2N [80JCS(CC)790].

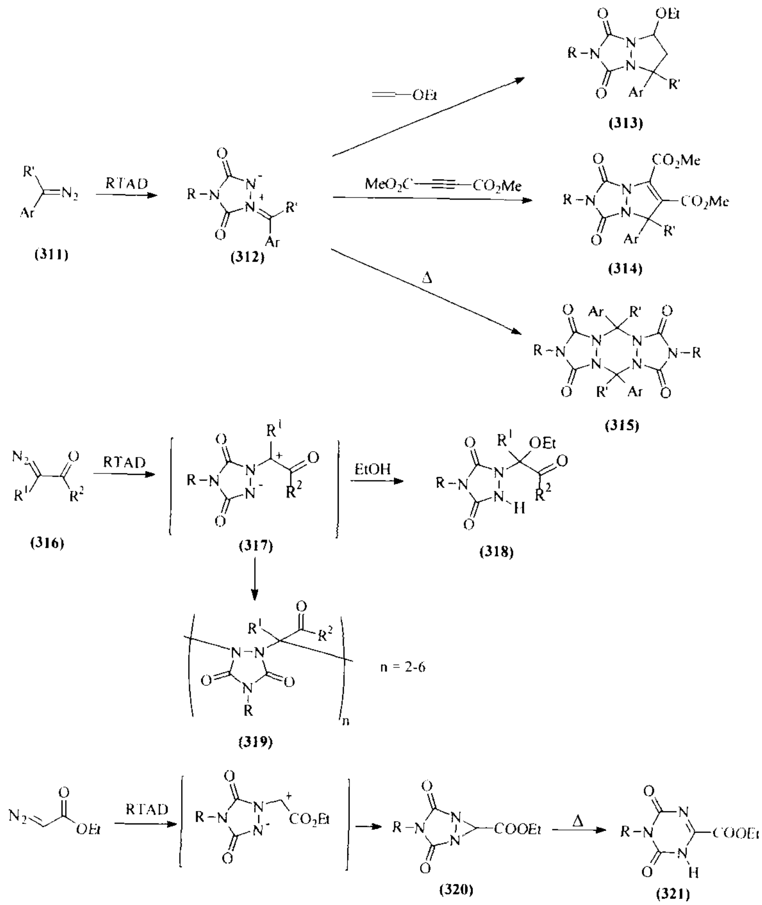
Stable azomethine imines **312** are formed by reaction of PTAD with aryl- or diaryldiazomethanes (**311**) (65G33, 65TL2553; 82ZOR1119; 85CB28; 91ZOR399). Similarly, stable azomethine imines are formed from some tricyclic diazo compounds derived from xanthene, thioxanthene (81TL2535; 82ZOR1986), anthrone, dibenzocycloheptane (81TL2535), and fluorene (73LA1141). Reaction of these azomethine imines with dipolarophiles, e.g., vinyl ethers or acetylene dicarboxylates, gave the corresponding bicyclic products **313** and **314**, respectively (73LA1141; 81TL2535; 82ZOR1986; 91ZOR399). Thermolysis of azomethine imines **312** gives dimeric compounds **315** (Scheme 54) (83KGS838).

Other azomethine imines of a general formula **317**, formed from diazo ketones **316** and TADs, are not isolable but can be trapped by alcohols to form the corresponding urazole derivatives, e.g., **318** (81TL2535).

Considerable confusion has existed with regard to the reaction of PTAD with diazoacetates. First, Izydore and McLean reported that this reaction gave the interesting bicyclic structure **320** (75JA5611). Korobitsyna *et al.* (81ZOR2021) and later other researchers (85T1965) reported that PTAD



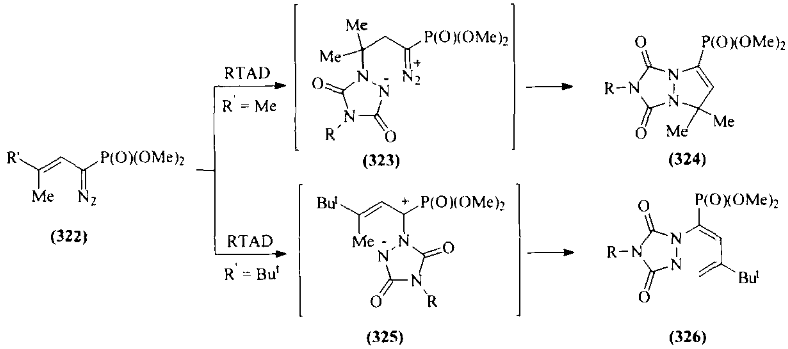
SCHEME 53



SCHEME 54

reacts with both alicyclic and cyclic α-diazocarbonyl compounds **316** to give oligomers **319.** Their series also included ethyl diazoacetate, and they concluded that previously published results were incorrect. However, a more recent paper of Izydore *et al.* again claims that **320** is formed in this reaction, and the structure is documented by two-dimensional NMR spectroscopy. Thermal isomerization of this product then provides triazinedione derivative **321** (Scheme 54) [88JCS(P2)1415].

Vinyl diazo derivatives **322** react with TADs, depending on the substituent pattern, either at the carbon double bond to give dipole **323,** or at the diazo carbon atom providing dipole **325** (Scheme 55). These dipolar intermediates then collapse into the final products **324** and **326,** respectively



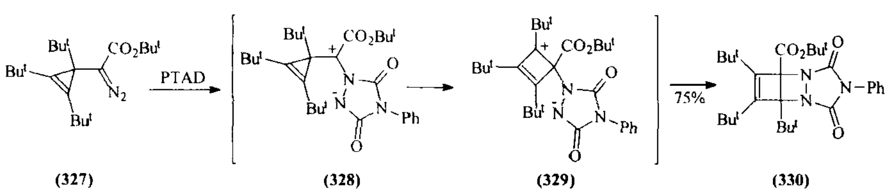
SCHEME 55

(85CB3396). Similar butadienyl diazo derivative **322** (R′ = vinyl) treated with TADs provides products of Diels–Alder addition without influencing the diazo substituent (85T2625).

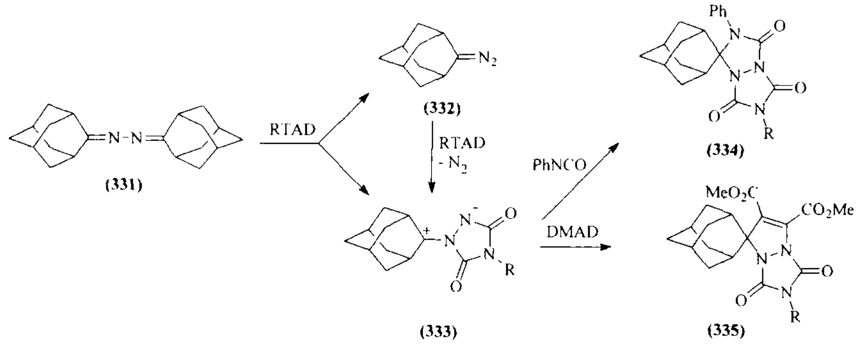
Cyclopropene diazo compound **327** treated with PTAD provides Dewar benzene analogue **330** in good yield (Scheme 56). Formation of this product is rationalized by way of intermediate dipolar urazole **328**, which then undergoes a 1,2 shift to dipolar species **329**, which collapses into the final product **330** (82CB3796).

Adamantanone azine (**331**) reacts with MTAD or PTAD under elimination of diazoadamantane (**332**) to give a 1,3-dipolar azomethine imine **333**. Diazoadamantane **332** then reacts with an additional molecule of TAD to give again **333** and nitrogen. Azomethine imine **333** can be trapped with phenyl isocyanate or dimethyl acetylenedicarboxylate as typical dipolarophiles to give **334** and **335**, respectively (Scheme 57) (84TL4757; 86T5273).

Diaryl acetylenes usually react slowly with TADs in solution at room temperature to give bis(azomethine imines) **336** as products (84JOC2917). 1,3-Diaryl isobenzofurans **337** with TADs give very stable betaines **338**, which do not undergo 1,3-dipolar cycloaddition [82JCS(CC)766]. Pyrido-[1,2-*a*]azepinone **339** treated with MTAD at room temperature gives a quantitative yield of a mixture containing mainly **342** accompanied by a



SCHEME 56



SCHEME 57

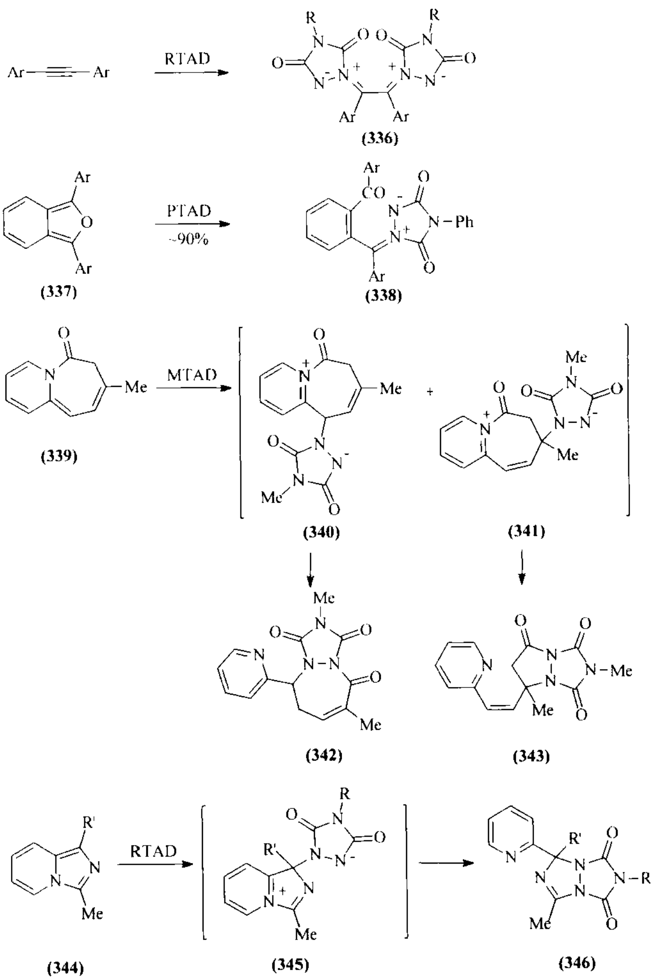
small amount of **343** (91HCA1095). Formation of these products is explained by dipolar intermediates **340** and **341**, respectively. The corresponding quinoazepinone reacts in the same way. Reaction of MTAD or PTAD with 3-methylimidazo[1,2-a]pyridines (**344**) gives compounds **346**, probably via dipolar intermediates **345** (Scheme 58) (95JHC1525).

Reaction of *N,N*-disubstituted hydrazines with PTAD gives amino azimines **347**. In the case of *N,N*-diphenyl hydrazine, the structure was determined by X-ray spectroscopy (73AG229). In the first step the *N,N*-disubstituted hydrazine is oxidized to the corresponding aminonitrene, which is then intercepted with PTAD to afford the dipolar azimines **347**, further thermally decomposed to **348** (70AG636; 72CJC1778; 80LA219).

Trichloromethyl dihydropyridines **350**, formed by treating pyridine quarternary salts **349** with potassium hydroxide in chloroform, add PTAD to give stable zwitterions **352**. Formation of these products can be easily explained by elimination of $CHCl_3$ from intermediates **351** (77CB2669).

Relatively stable dipolar compounds, e.g., **354**, the structure of which was determined by X-ray spectroscopy, are accessible by treating arylthioxodithianes **353** with PTAD. A labeling experiment has indicated that the reaction involves loss of the exocyclic sulfur atom (77ZOR2012; 79IZV545; 80ZOR198; 84ZOR1562). 1,3-Dipolar addition of dimethyl acetylenedicarboxylate to this ylide under rather forced conditions leads to pyrazolo[1,5-*b*]isothiazoles **355** (Scheme 60) (84ZOR1562).

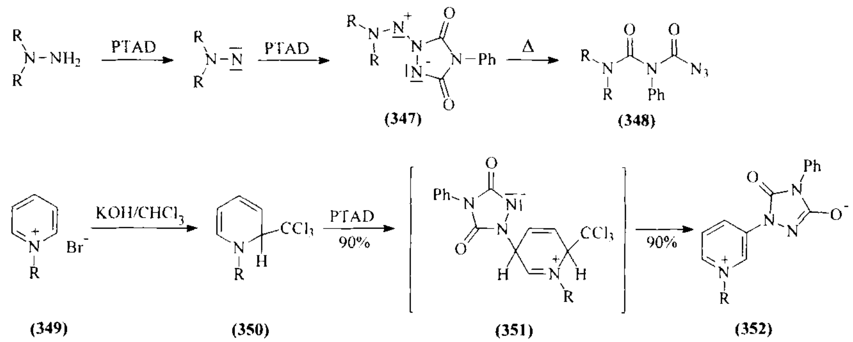
2-Alkylidene-1,3-oxathiole **356** treated with excess of PTAD gave a mixture containing 64% of zwitterion **360**, 12% of tetrazolidine **362**, and 15% of thioketene **363** (89TL1249). This result suggests a possible equilibrium of **356** with ring-opened thioketene *S*-methylide **357** and its charge-delocalized betaine **358**. These two intermediates trapped with PTAD could provide **359** and **361**, respectively. Reaction of these possible intermediates with



SCHEME 58

an additional molecule of PTAD then can provide the final products (Scheme 60).

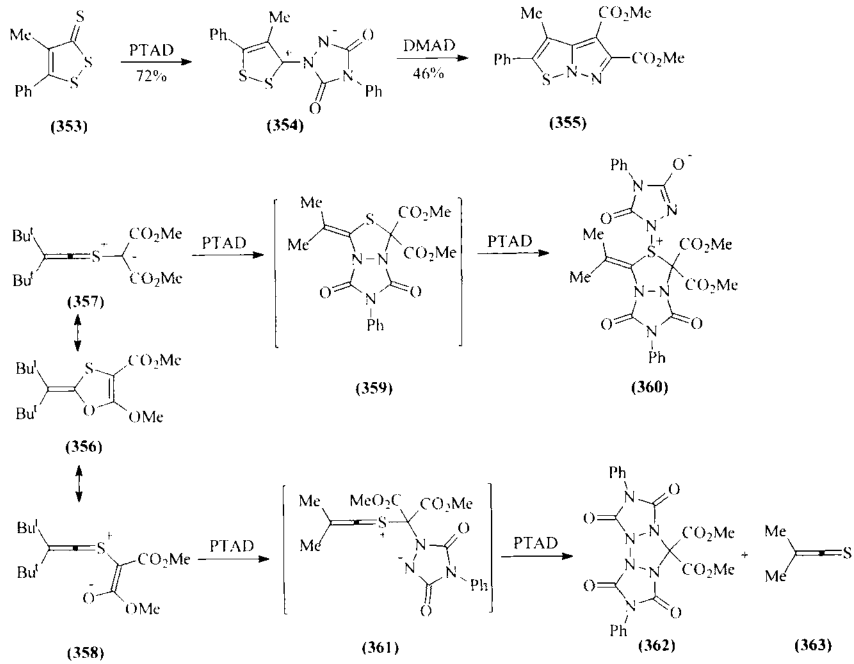
PTAD adds to a variety of carbonyl compounds to form α-urazolylcarbonyl products; see Section IV,I. Refluxing a benzene solution of tetraacetylethylene (**364**) with PTAD gives hetero spirane **367** (89T7929). Formation of this structure can be rationalized by a dipole–carbanion species **365** formed from **364** and PTAD, which in this case behaves as a base. Intermediate **365** then reacts with a further molecule of PTAD in a con-



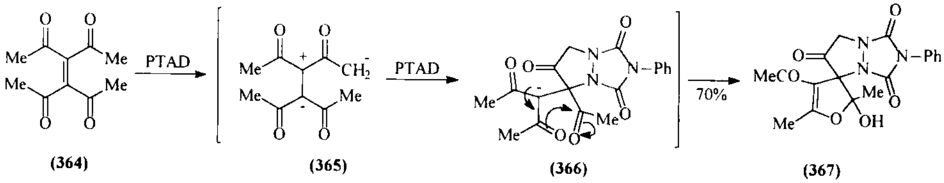
SCHEME 59

certed reaction to provide anion **366**, which then affords the final product **367** (Scheme 61).

Many other reactions of TADs are also explained by 1,4-dipolar intermediates. Selected examples are given in Scheme 62. Thus, bicyclopropylene **368** with PTAD at 0°C gives cyclic dipolar intermediate **369**, which then



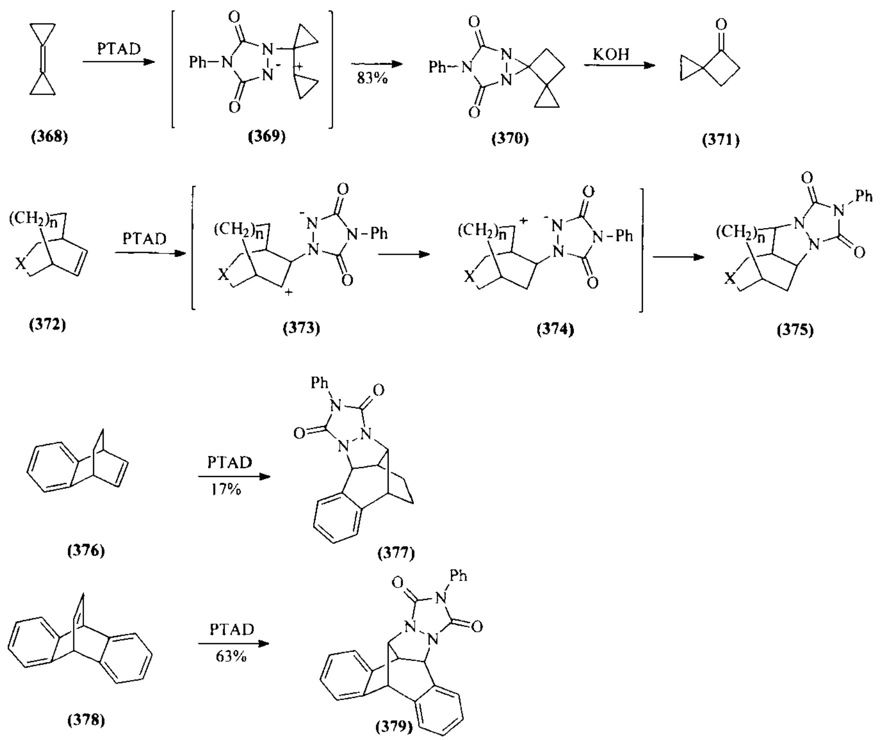
SCHEME 60



SCHEME 61

collapses with ring enlargement to **370.** This compound can be easily hydrolyzed under alkaline conditions to spiro ketone **371.** The same product is directly obtained in good yield when the reaction of **368** with PTAD is performed in wet acetone (80AG387; 88JOC152).

Cycloaddition of PTAD with strained bicycloalkenes **372** often leads to tricyclic urazoles **375.** A key feature of the proposed mechanism is an initial attack of PTAD resulting in 1,4-dipolar intermediate **373,** which



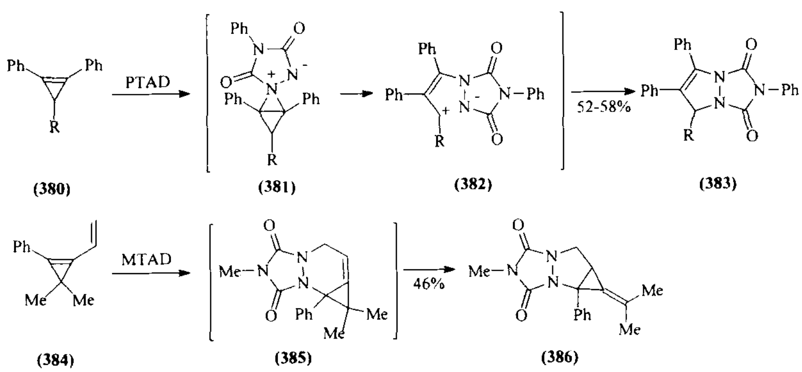
SCHEME 62

subsequently rearranges to **374** and collapses to product (79AG512, 79TL4367; 80AG815, 80JA4806; 81JA2496; 86S854). The reaction requires an elevated temperature and about a threefold excess of PTAD because of its extensive degradation under the harsh conditions. The reaction is nearly general for many strained bicyclic systems, e.g., for derivatives of bicyclo[2.2.1]hept-2-ene. Interestingly, simple bicyclo[2.2.2]oct-2-ene does not react even after 2 weeks of reflux in acetonitrile (79TL4367). Its benzo and dibenzo derivatives **376** and **378** provide the rearranged products **377** and **379**, respectively. In case of the mono benzo derivative **376**, only compound **377** is formed (79TL4367).

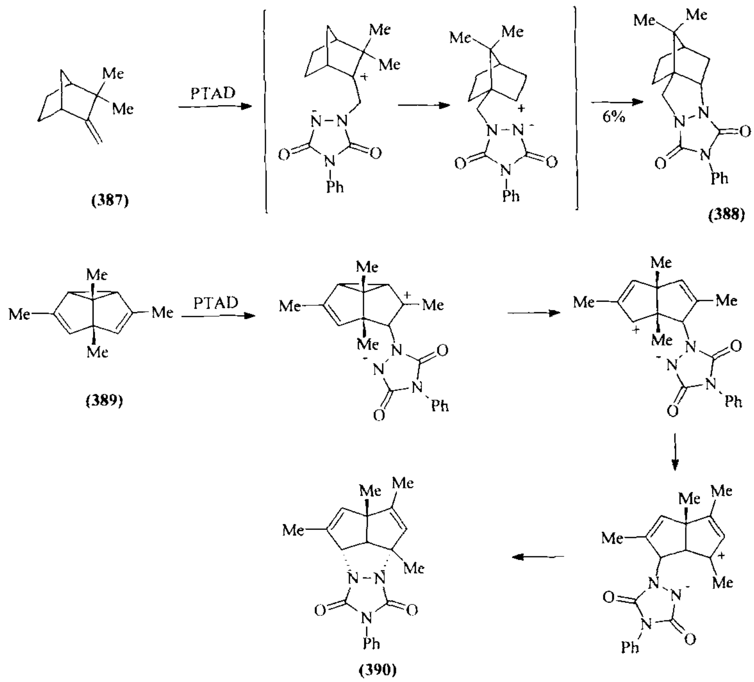
Reaction of 1,2-diphenylcyclopropene derivatives (**380**) with PTAD gives bicyclic derivatives **383**. Aziridine intermediate **381** is expected to rearrange to dipole **382**, which then collapses to the final product (Scheme 63). Cycloaddition of MTAD to similar vinylcyclopropene **384** proceeds in a different way, providing **386**. Formation of this product can be rationalized in terms of an initial formation of the Diels–Alder adduct **385**, which then rearranges by a 1,3-sigmatropic shift to thermodynamically more stable compound **386** (90JOC2478).

An interesting rearrangement of an intermediate 1,4-dipole takes place in the reaction of TADs with camphene (**387**), which provides a low yield of **388** (82CB1982).

A 1,4-dipolar intermediate is initially formed also in the reaction of PTAD with semibullvalene derivative **389**. The reaction proceeds via several dipolar structures and finally provides tetracyclic compound **390** (Scheme 64). The reaction is described also for several other semibullvalene derivatives (75TL1549; 76TL3891). Usually, the corresponding products of a Diels–Alder type of addition to the vinylcyclopropane system are present.



SCHEME 63

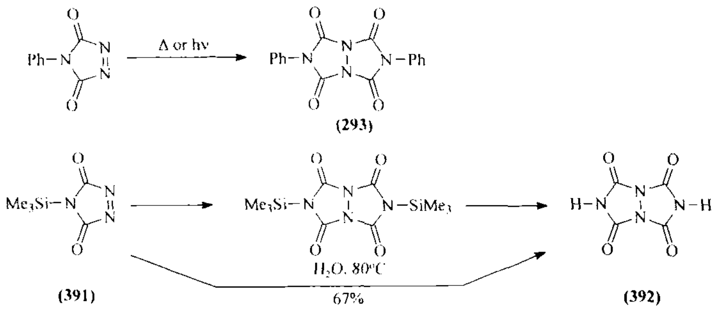


SCHEME 64

For example, symmetrical octamethylsemibullvalene gives a mixture containing about 50% of both components (75TL1549; 76TL3891).

G. DIMERIZATION

1,2,4-Triazolo[1, 2-*a*][1,2,4]triazole **293** has been reported to be a decomposition product of PTAD under photolytic or thermal conditions in various solvents [12CB273; 76JCS(CC)326; 77CB1699; 79CJC2727; 84JOC2579; 85JOC4589; 86JOC1563; 88AG703]. The catalytic activity of several agents has been described [76JCS(CC)326; 80ZOR2444; 86JOC1563], and in some instances, e.g., with catalysis by potassium *tert*-butoxide in DMSO, the yields are nearly quantitative. Similarly, thermolysis of other *N*-substituted TADs provides mixtures from which low to moderate yields of the corresponding symmetrically substituted tetraoxo triazolo[1,2-*a*][1,2,4]triazoles can be isolated (75JOC1854). For the synthesis of *N*-unsubstituted derivative **392**, protection of the nitrogen atoms is necessary. The compound is prepared in 67% yield from *N*-trimethylsilyl precursor **391** (Scheme 65) (88AG703).



SCHEME 65

H. OXIDATION

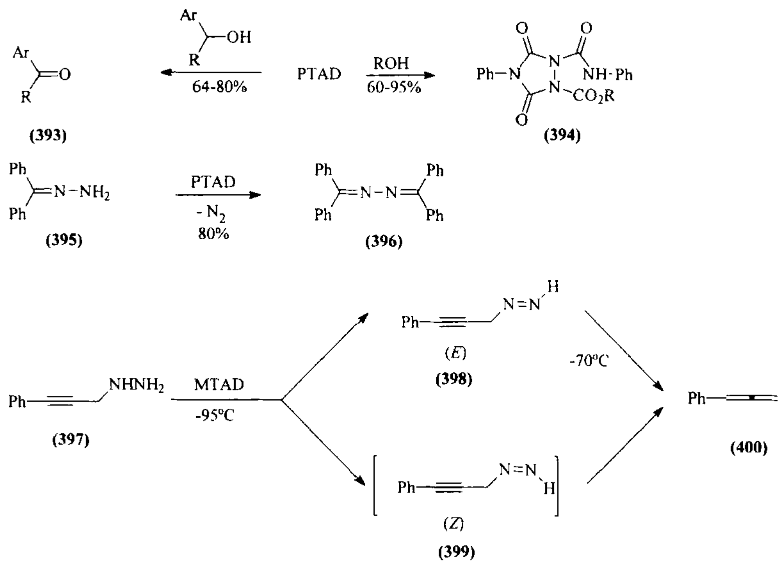
PTAD has been used to oxidize alcohols to the corresponding carbonyl compounds **393** with formation of 4-phenylurazole [66JCS(CC)744; 76-JCS(CC)326; 79CJC2727]. This method is effective only with easily oxidizable alcohols, especially arylalkylmethanols. Medium yields of the carbonyl compounds can be obtained also from 2-propanol or cyclopentanol. However, simple primary alcohols provide high yields of urazoles **394**, which are formed from two molecules of PTAD (Scheme 66) [76JCS(CC)326; 86JOC1563; 87JOC1288].

Only a few other examples of the oxidative properties of PTAD have been reported. Benzophenone hydrazone (**395**) is oxidized to the corresponding azine (**396**) and nitrogen (72T4939). (3-Phenyl-2-propynyl)hydrazine (**397**) is oxidized with MTAD to a mixture of both possible diazene isomers **398** to **399**. These isomers undergo [3,3]-sigmatropic elimination of nitrogen (retro-ene reaction) to provide allene **400.** The (*Z*)-isomer **399** rearranges at low temperature and cannot be observed, whereas the (*E*)-isomer **398** is observable by NMR spectroscopy at −95°C, undergoing the elimination at −70° (90JA9641). 1-Methyl-3-phenylallene can be prepared by the same method (Scheme 66) (89TL5747).

Oxidation of *N*,*N*-disubstituted hydrazines with TADs to the corresponding aminonitrenes may be the first step of the reaction leading to amino azimines. The reaction is covered in Section IV,F.

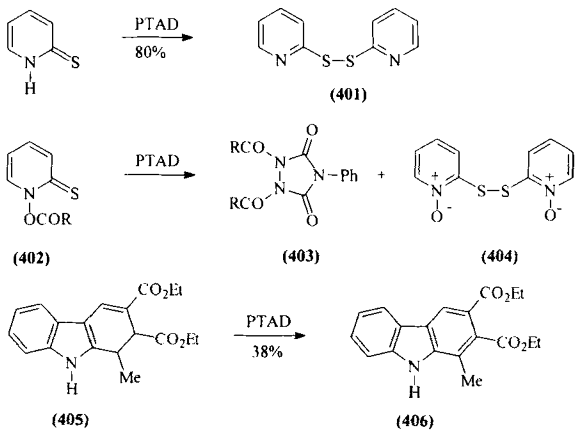
N-Unsubstituted 2-thioxopyridines give the corresponding disulfides, e.g., **401** (80ZOR2444). Esters of *N*-hydroxy-2-thiopyridine (**402**) treated with PTAD give diacylurazoles **403** and disulfide **404** (88T7385).

Dihydrocarbazole **405** treated with PTAD does not provide the expected Diels–Alder adduct, but a dehydrogenation reaction leading to **406** occurs instead (Scheme 67) (91LA357). Similarly, the Diels–Alder product of addition of PTAD to 1-methyl-2-(1-phenylvinyl)indole corresponding to



SCHEME 66

compound **84** is oxidized by PTAD to the corresponding heteroaromatic species as a final product [88H(27)967]. However, other authors reported that the corresponding Michael-type product (see Section IV,I) is formed under similar conditions [87H(26)401]. Similar oxidative aromatization of the Diels–Alder adducts of PTAD to perylene and similar polycyclic aro-

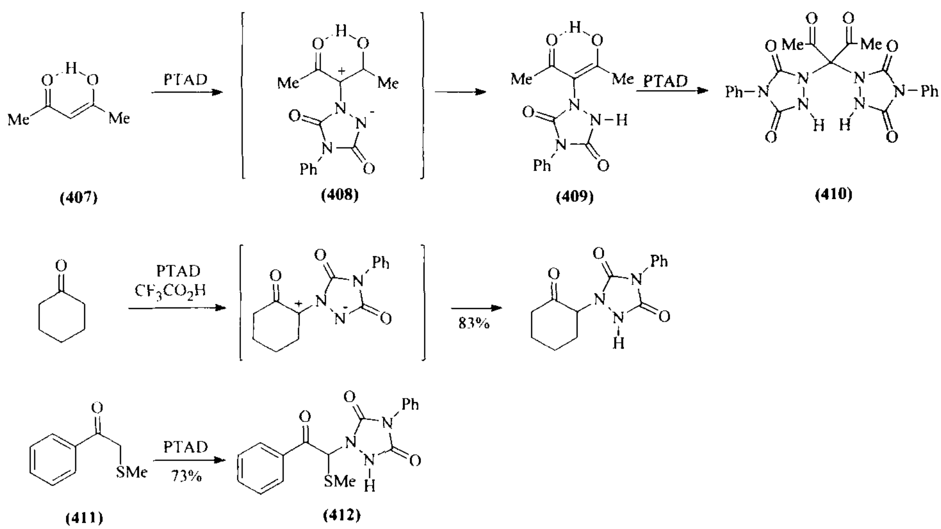


SCHEME 67

matic compounds is expected to take place during these reactions (see Section IV,A,3).

I. Reactions with Nucleophiles

With highly enolizable carbonyl systems, this type of substitution reaction can occur rapidly even in the absence of a catalyst. β-Diketones, e.g., **407,** react with PTAD to form either 1:1 adducts **409** or the corresponding 2:1 adducts **410,** depending on the excess of the diketone. Since a kinetic preference for the 2:1 adduct has been observed, it is necessary to use a relatively high excess of the diketone to obtain the 1:1 adduct. Kinetic studies support a reaction pathway through the 1,4-dipolar intermediate **408** formed by the reaction of TAD with the enol form of the dicarbonyl compound (80JOC1232). Selected examples of the reaction are shown in Scheme 68. With simple carbonyl compounds, both cyclic and acyclic, the presence of an acidic catalyst such as trifluoroacetic acid is necessary (90JOC193). Unsymmetrical ketones afford a mixture of both urazolyl ketones. The initially formed monourazoles can usually be further transformed to the corresponding bis derivatives by using additional PTAD. Reaction of acetophenone and deoxybenzoin under these conditions gave 57% and 65% yields of the respective monoadducts. Acetophenone deriva-



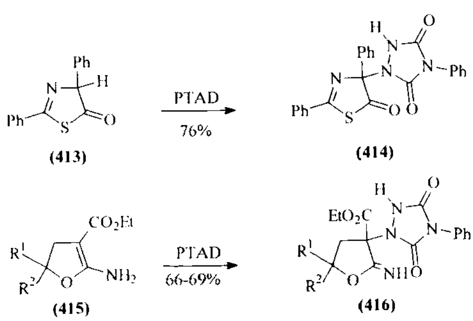
Scheme 68

tive **411** treated with TADs affords the expected Michael-type monoadduct **412** in good yield (82TL3909).

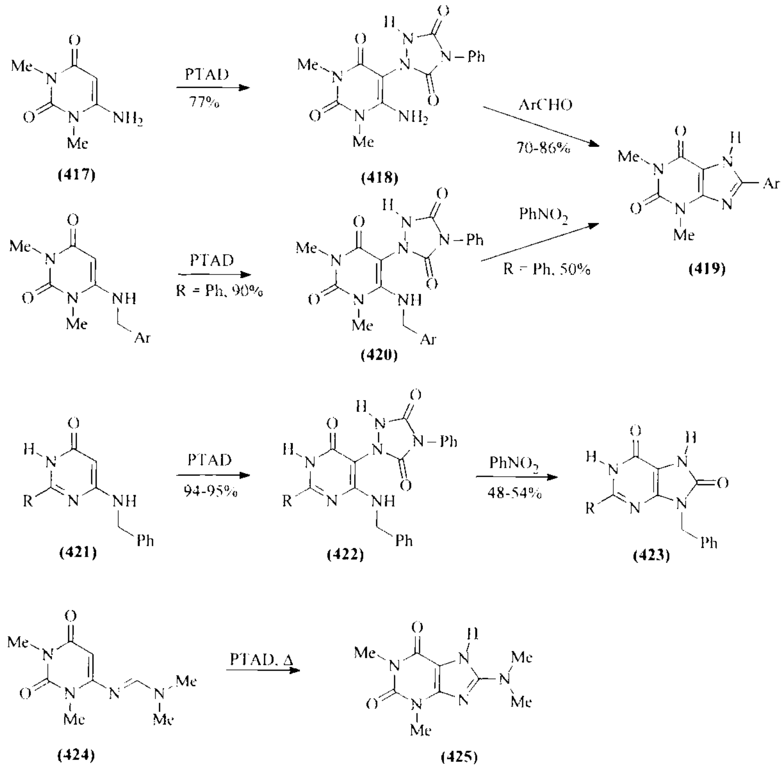
2,4-Diphenylthiazolone (**413**), possessing an acidic hydrogen atom, gives with PTAD a product of Michael addition (**414**) (76T571). Similarly, dihydrofuran derivatives **415** give adducts **416** (Scheme 69) (77CB1716).

Treatment of various 4-oxopyrimidines with PTAD gives the corresponding Michael-type adducts (77CB1716). When such an adduct **418,** formed from 6-aminopyrimidine **417,** is treated with aromatic aldehydes, the reaction affords purine derivatives **419** [74JCS(CC)551; 77JCS(P1)2285]. Similarly, oxidative cyclization of PTAD adduct **420** with nitrobenzene gives **419.** Michael-type adducts **422,** obtained from 4-oxo-6-benzylaminopyrimidines **421** and PTAD, upon oxidation provide 9-benzylpurines **423** [77JCS(P1)-2285]. Uracil derivative **424** treated with PTAD gives an intermediate similar to **420,** which thermally cyclizes to 8-dimethylaminotheophylline (**425**) (88TL4401; 89CB1673). By means of this approach a wide variety of purine derivatives can be prepared (Scheme 70). PTAD serves as a nitrogen source for *N*-7 of the purine ring system.

TADs also react with some electron-rich nitrogen heterocycles that act as nucleophiles. *N*-Methylpyrrole and *N*-methylindole treated with an excess of TADs give bis adducts **426** and **427,** respectively (84JOC2579). 2,2′-Bis-indoles treated with PTAD gave similar adducts (92AP353). Charge-transfer complexes of TADs with*N*-methylpyrrole are said to be intermediates. The urazolyl radical may catalyze this reaction. 2-Vinylindoles usually give with TADs the corresponding Diels–Alder adducts (see Section IV,A,3). However, 1-methyl-2-(1-substituted vinyl)indoles are reported to provide medium to good yields of the corresponding Michael-type adduct containing a urazole ring at position 3 [87H(26)401]. Indole itself and its 1,2-unsubstituted derivatives treated with PTAD give polymeric material, but 2-methylindole provides the corresponding 3-urazolyl derivative.



SCHEME 69

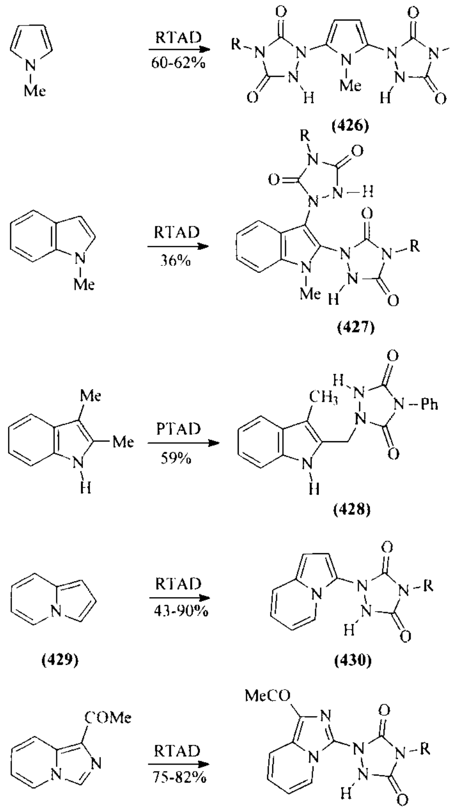


SCHEME 70

2,3-Dimethylindole treated with PTAD gives urazole **428** (85TL3673; 87JOC2699).

A similar addition reaction has also been reported for indolizine (**429**), which upon treatment with TADs gives monoadduct **430** [79H(12)787]. Similarly, 1-acetylimidazo[1,5-*a*]pyridine (**431**) gives with both MTAD and PTAD the corresponding Michael-type adducts **432.** In contrast, unsubstituted imidazo[1,5-*a*]pyridine, an aza analogue of **429,** gives with TADs a 2:1 adduct (95JHC1525).

A similar reaction is observed also with electron-rich polyalkoxybenzenes, such as 1,3,5-trimethoxybenzene and 1,3- and 1,4-dimethoxybenzene (Scheme 72). For example, 1,3,5-trimethoxybenzene with PTAD provides urazole **433** (83JOC1708). Anisole reacts with PTAD only under photochemical conditions to give **434,** among other products (77CB1699). Tropolone (**435**), unlike tropone itself (see Section IV,A,2), gives addition product **436** [70JCS(CC)82; 71JCS(C)2142]. Arylated urazoles, e.g., **437,** derived



(426)

(427)

(428)

(429) (430)

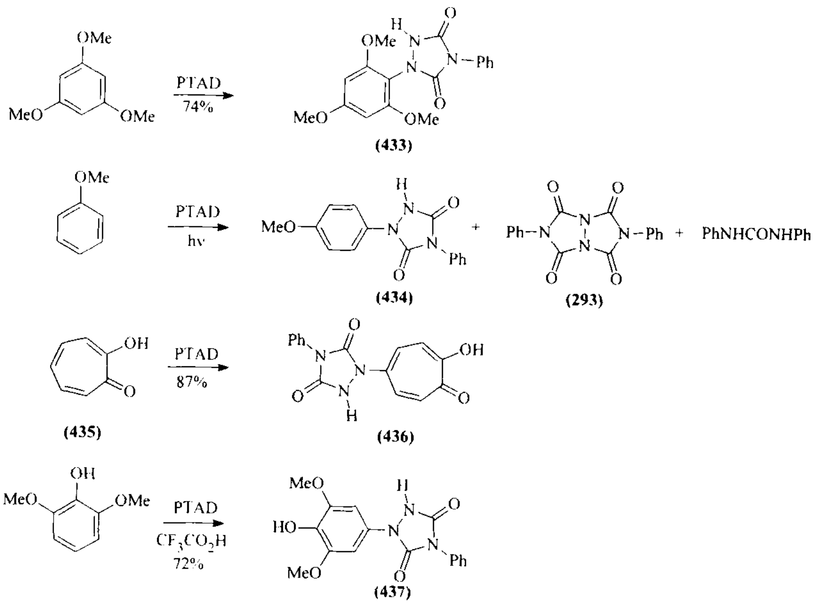
(431) (432)

SCHEME 71

from some suitably substituted phenols can be prepared by the reaction of PTAD catalyzed with trifluoroacetic acid. Similarly, suitable 2,4-disubstituted phenols provide the corresponding 2-urazolyl phenols (Scheme 72) (91JA2301).

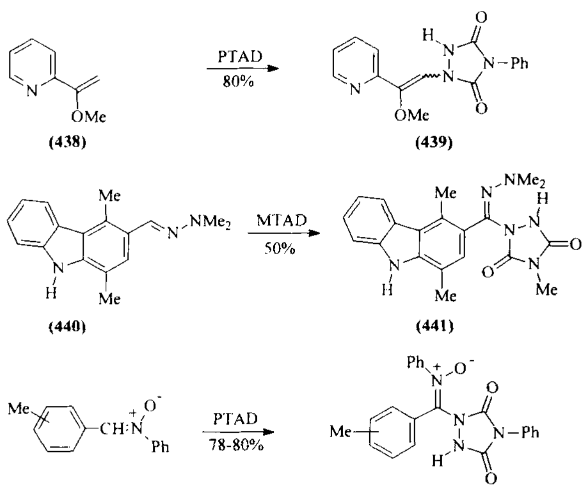
Reaction of TADs with *N,N*-dimethylaniline provides, without any catalyst, products of electrophilic aromatic substitution at the *para* position [89JPS(A)125].

α-Methoxyvinylpyridine (**438**), unlike similar vinyl- or bromovinylpyridines (see Section IV,A,3), upon treatment with PTAD gives product **439** (78KGS651). Dimethyl hydrazone **440** provides urazole **441** [90H(31) 1927]. Nitrones **442** treated with PTAD give none of the expected 1,3-dipolar addition products, but compounds **443** are obtained exclusively (Scheme 74) (83JPR908).



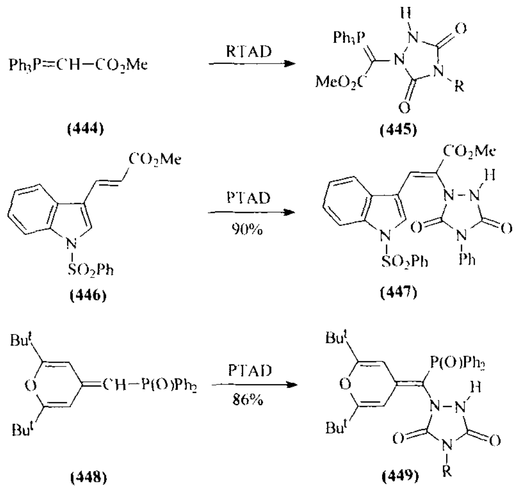
(433) (434) (293) (435) (436) (437)

SCHEME 72



(438) (439) (440) (441) (442) (443)

SCHEME 73



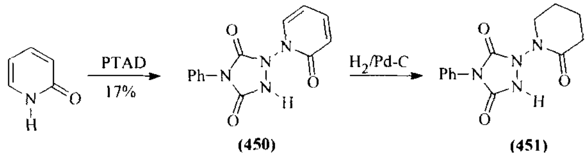
SCHEME 74

Alkylidenetriphenylphosphorane **444** gives with TADs the corresponding adducts **445** (83MI1). Similar double bond activation has been observed with 3-vinylindole **446** (90C339) and pyran derivative **448** (84CB2233), which, when treated with PTAD, gave **447** and **449**, respectively.

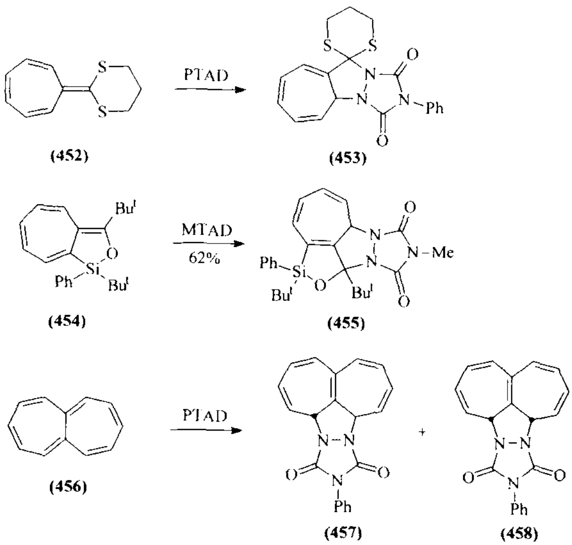
Unlike *N*-substituted 2-pyridones, which provide with TADs the corresponding Diels–Alder adducts (see Section IV,A,4), 2-pyridone itself provides with PTAD a low yield of **450**, a product of addition of PTAD to the NH function of the pyridone (76JHC673; 77DOK606). Catalytic reduction of this compound then easily affords the corresponding tetrahydro derivative **451** (76JHC673).

J. MISCELLANEOUS REACTIONS

In some cyclic polyenes a relatively rare [8 + 2] cycloaddition of PTAD has been observed (Scheme 76). Electron-rich trimethylene-8,8-



SCHEME 75

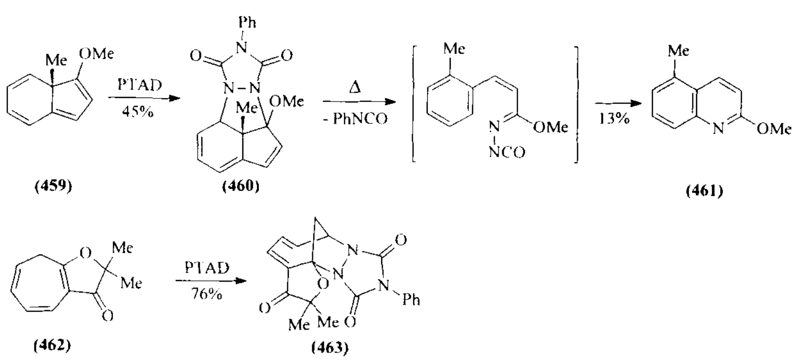


SCHEME 76

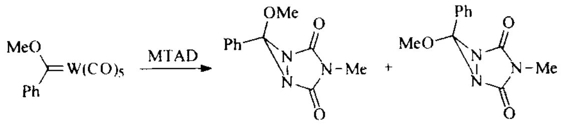
dithiaheptafulvene **452** reacts in this way to give spiro compound **453** (76-TL2011). Similarly, **454** treated with MTAD gave **455** [86JCS(CC)1782].

Heptalene (**456**) reacts with PTAD to provide a mixture of both possible isomers **457** and **458** in which **457** strongly prevails (79AG581).

3a*H*-Indene **459**, generated *in situ*, could be intercepted by PTAD to give a 45% yield of **460** [80JCS(CC)689; 81JCS(P1)3214]. The addition can also be defined as a [2 + 8] cycloaddition to the tetraene system. Attempts to regenerate the starting tetraene by flash vacuum pyrolysis led to quinoline **461** by a pathway outlined in Scheme 77 [81JCS(P1)3214]. A similar bicyclic



SCHEME 77



(464) (465) (466)

SCHEME 78

polyene, 4a*H*-benzocycloheptene, gave a typical Diels–Alder adduct with the cyclohexadienyl part of the structure [79JCS(CC)528].

Cycloheptatriene furanone **462** treated with PTAD gives **463,** a product of an unusual [6 + 2] cycloaddition [87H(26)2339].

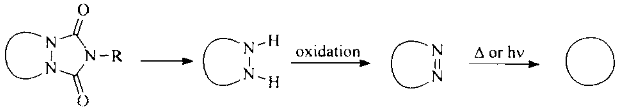
Interestingly, reaction of pentacarbonyl complex **464** with MTAD in acetonitrile resulted in formation of two isomeric diaziridine derivatives **465** and **466** (Scheme 78) (91OM1913).

K. MISCELLANEOUS SYNTHETIC APPLICATIONS

1. *Preparation of Cyclic Azoalkanes and Their Transformations*

Cyclic azoalkanes continue to be of active interest because they serve as precursors to interesting diradicals and as synthons for the preparation of highly strained ring systems and sterically crowded structures. One of the most important syntheses of the azoalkanes involves the cycloaddition of TADs to a suitable substrate to give urazoles by a method mentioned in preceding parts of this review. These methods include Diels–Alder, homo Diels–Alder, and domino Diels–Alder addition, as well as the ene reaction, 1,2-cycloaddition, or other types of cycloaddition reactions. These adducts are transformed into cyclic azoalkanes by hydrolysis an oxidation. The azoalkanes are very often used for thermal or photochemical decomposition to cyclic compounds. This sequence is outlined in Scheme 79.

One of the serious disadvantages of the use of TADs is the difficulty of hydrolyzing such urazoles as **467.** Very often the harsh conditions (strong base, high temperature) provide low yields of the cyclic hydrazines **468** and



(467) (468) (469) (470)

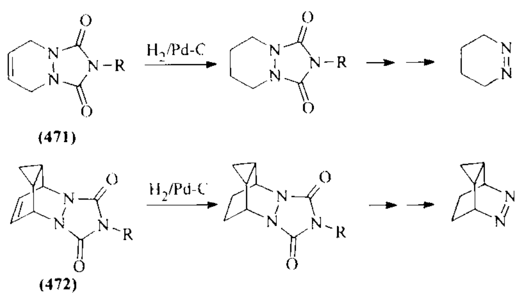
SCHEME 79

they are not compatible with sensitive functionalities. Sometimes hydrazinolysis can overcome this drawback, but the method does not seem to be generally applicable (81S543). Cyclic hydrazines **468** formed in the first step are easily oxidized into the azoalkanes, the most commonly used reagent being copper(II) chloride. The oxidation provides the corresponding copper(I) complex of the azo compound, which is easily decomposed into the parent azoalkane under alkaline conditions [72OSC(5)96]. Azo compounds **469** are often thermally or photochemically decomposed to give the corresponding cyclic compounds **470,** mostly unavailable by other methods. The mechanism and scope of the thermal and photochemical decomposition of azoalkanes has already been reviewed extensively (77AG876; 80AG815, 80CRV99), and this area is not covered in detail in this article.

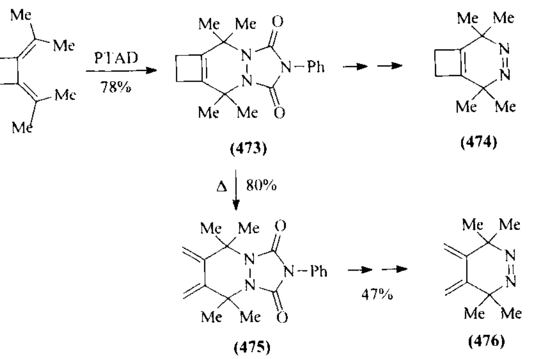
Often the Diels–Alder TAD adducts are first hydrogenated and then submitted to the preceding sequence, shown in Scheme 80 for cyclic urazoles **471** and **472** (69CB811).

Cycloadducts formed from TADs are often modified and then subjected to the hydrolysis–oxidation procedure. For example, hydrolysis and oxidation of **473,** the initial PTAD adduct to 1,2-diisopropylidenecyclobutane, gives labile azoalkane **474.** However, thermal isomerization of the initial cycloadduct give **475,** which then provides **476** in the usual way (Scheme 81) (76JA1875).

Another example of the modification of the initial Diels–Alder adduct is shown in Scheme 82. Bicyclic dibromide **477** provides with PTAD the corresponding cycloadduct **478,** which after debromination affords **479.** Further treatment with 2-pyrone proceeds with the evolution of carbon dioxide to give cycloadduct **480,** which in the usual way provides **481** (72JA3658). Intermediate **479** can be photochemically isomerized to give a diazabasketane derivative **482,** which then, by a well-known sequence, can provide diazabasketane **483** (74JA7454; 77JA1524). The Ag^+-catalyzed rearrange-



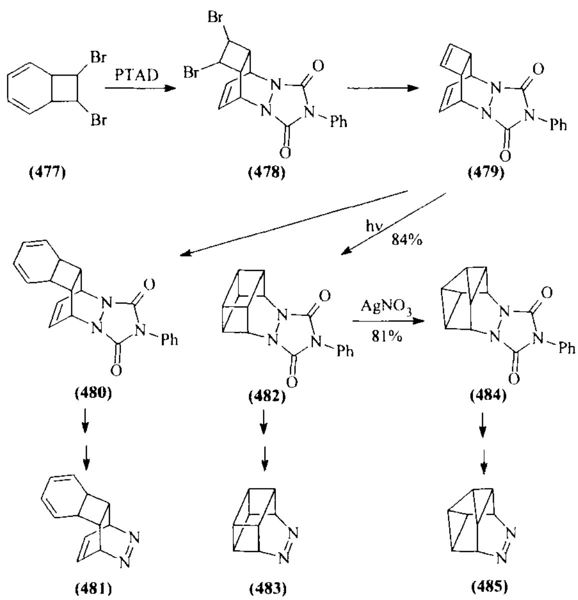
SCHEME 80



SCHEME 81

ment of the diazabasketane precursor **482** provides **484,** which then gives diazasnoutane (**485**) (74JA7465).

In most cases thermal or photochemical treatment of the azoalkanes is a pathway to the corresponding alkanes via the corresponding diradicals. This aspect is extensively covered by the reviews already cited. However, in some cases, the diradicals collapse in a different way. For example, Diels–Alder addition of cyclopentene derivative **486** to MTAD gives ura-



SCHEME 82

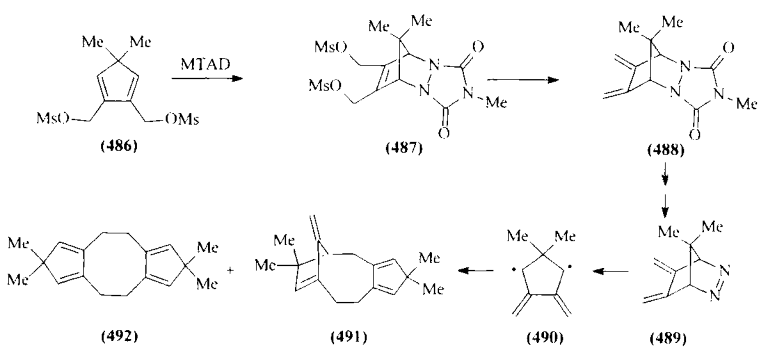
zole **487,** which upon treatment with sodium iodide affords **488.** The usual treatment then provides azo compound **489,** a suitable source of diradical **490,** which then provides a mixture of tricycles **491** and **492** (Scheme 83) (87AG1330).

A wide variety of unusual structures has been prepared under gentle conditions by employing nitrogen extrusion as a last synthetic step. Formally similar pericyclic thermolytic extrusion of N_2O from polycyclic azoxy systems has also been described (Scheme 84) [72JCS(CC)867; 74JA7839; 77JA1524]. These compounds are available by oxidation of azo compounds with hydrogen peroxide or MCPBA (74JA5158), but usually are prepared directly from suitable TADs adducts, e.g., **493, 495,** and **476,** by treatment with high concentrations of potassium hydroxide and hydrogen peroxide. Bicyclic azoxy derivative **494** decomposes quantitatively to cycloheptatriene at temperatures slightly above ambient. However, similar azoxy derivatives **496** and **498** required temperatures above 100°C to give quantitative yields of cyclooctatriene and cyclooctatetraene, respectively (74JA7839; 77JA1524).

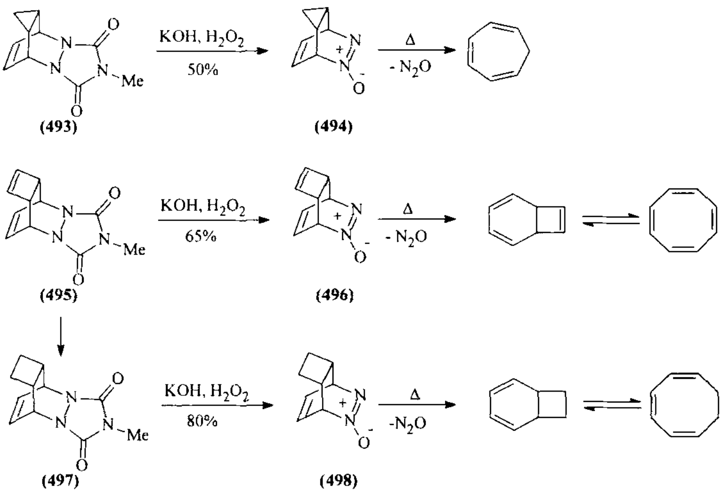
A different photochemical reaction of **499** leading to bicyclic structure **500** has been observed [72JCS(CC)867]. In contrast, other constrained bicyclic azoxy compounds lacking the cross-ring nitrogen atoms, which are present in **499,** do not react in this way.

2. *Preparation and Use of Triazolinedione Ylides*

Stable triazolinedione ylides have been isolated from the reaction of TADs with appropriately substituted diazo derivatives, isobenzofurans, and acetylenes. Reaction of azomethine imines prepared by this way with ethylenic dipolarophiles, e.g, vinyl ethers or acetylene dicarboxylates, gives the



SCHEME 83

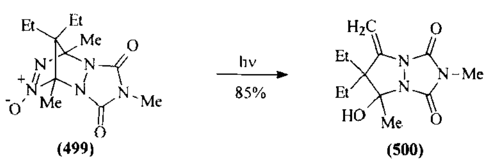


SCHEME 84

corresponding bicyclic products (82ZOR1986; 91ZOR399), as demonstrated in Section IV,F.

This method of preparation of ylides from the corresponding triazolinediones is limited in its synthetic utility. Oxidation of suitable urazolyl compounds seems to be a much more versatile entry to this class of highly reactive dipolar compounds. Starting substituted urazoles are often readily available by simple nucleophilic substitution reactions of urazoles with suitable alkyl halides. As is evident from the preceding sections, many other substituted urazoles can be prepared by the ene-type reaction of TADs, by the reaction of TADs with ketones, or by their electrophilic aromatic substitution reactions. Oxidation of these urazoles, e.g., **501, 428, 504,** and **506,** can be effected with *tert*-butyl hypochlorite, or, in some cases, excess PTAD can be used. Various approaches and utilization of this synthetic strategy are best seen in the following examples.

Triazolinone ylides **502, 503, 505,** and **507** trapped with alcohols give the corresponding urazole derivatives, which can be further hydrolyzed to 4-

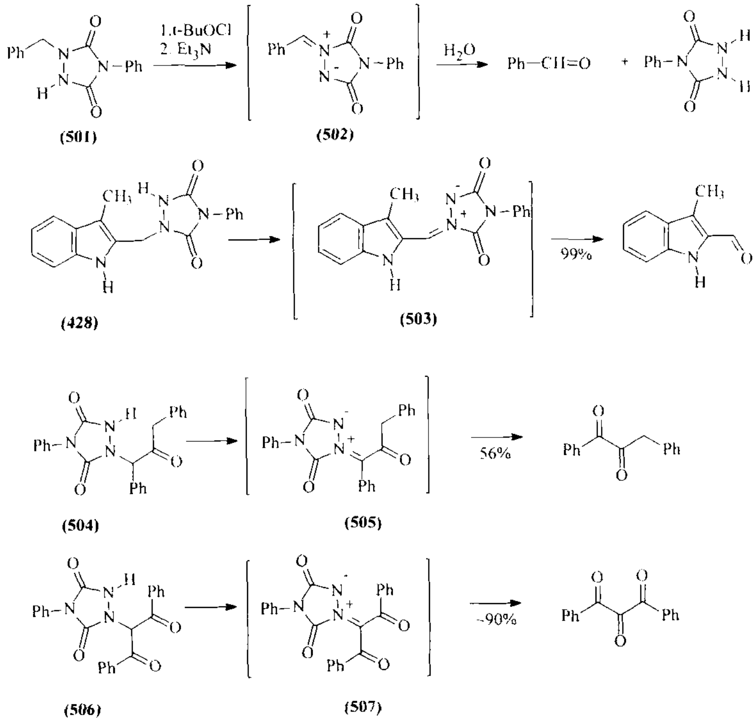


SCHEME 85

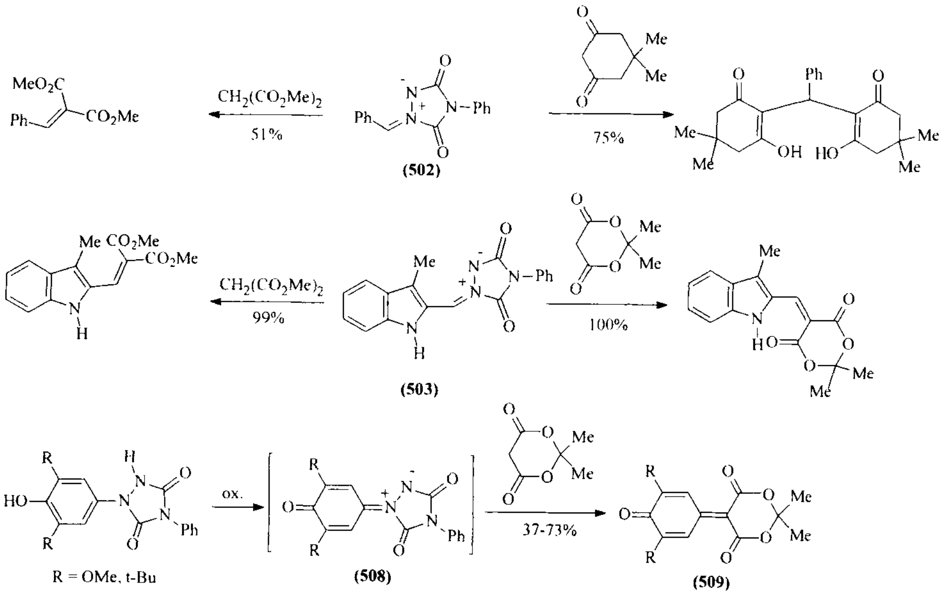
phenylurazole and the corresponding carbonyl compounds (81TL2535; 85T1965; 90JOC197). This approach has been used for the preparation of various aldehydes, ketones, α-diketones, and even triketones as shown in Scheme 86 (87JOC2699; 901JOC197).

Some triazolinedione ylides have been used as extremely reactive carbonyl equivalents. Their reaction with various compounds possessing an active methylene group provides the expected products, usually in high yields. Selected examples are given in Scheme 87. In some cases, e.g., in the reaction of dipole **502** with dimedone, bis adducts are formed. However, dimethyl malonate gives with the same species the corresponding monoadduct (87JOC2699). If ylides **508,** derived from suitably substituted phenols, are used, the corresponding quinone methides **509** are obtained. Ortho quinone methides can also be prepared via the corresponding ortho dienone ylides formed from ortho urazolyl phenols (91JA2301).

The electron-rich double bonds of pyrrole are also sufficiently nucleophilic to react with triazolinedione ylides to give the corresponding bis adducts, e.g., **510.** Reaction of this type of ylides with thiols is also described.



SCHEME 86

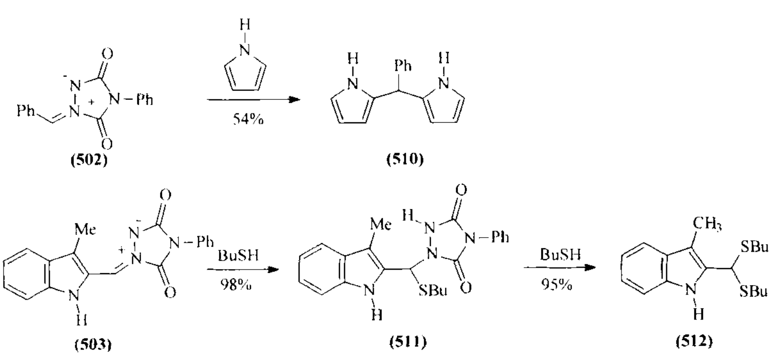


SCHEME 87

For example, ylide **503** treated with butanethiol initially gives compound **511,** which when treated with excess thiol gives bis adduct **512** (87JOC2699).

3. *Use of Triazolidinones in Polymer Chemistry*

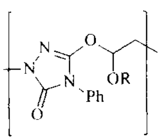
TADs can be used in polymer chemistry in several different ways. Simple TADs, e.g., PTAD, copolymerize with other components. Ethyl vinyl ether



SCHEME 88

and divinyl ether spontaneously polymerize with PTAD to give copolymers **513** [71JPS(B)115]. Vinyl carbamates provide **514** analogously [72JPS(B)1]. PTAD is able to copolymerize with vinyl carbazole, but does not form polymers with styrene or divinyl carbonate (73MI1). Treatment of styrene with PTAD gives a bis-Diels–Alder adduct and Diels–Alder-ene adduct (see Section IV,A,3). Polymerization of styrene has been achieved with some bis-TADs, providing polymers containing the corresponding units **515** and **516** (72MI2). Bis-TADs studied for their use in polymer chemistry include compounds having aliphatic chains, e.g. hexamethylene, or various combinations of aromatic and aliphatic parts such as diphenylmethanediyl derivatives, or aromatic chains, including diphenyl etherdiyl derivatives (72MI1; 79MI2; 85MI1). Bis-TADs also form polymers with *N*-methylpyrrole to afford **517** [87JPS(A)2781]. Divinyl esters, e.g., divinyl adipate, form with bis-TADs polymer structures **518** via a 1,4-dipolar rearrangement (79MI1, 79MI2).

Several TADs have also been studied as low-temperature modifiers of dienic polymers, especially butadiene homo- and copolymers. Isolated double bonds in these polymers react in the same sense as in the ene reaction (Scheme 90) to give urazole-substituted polymers **519** (79MI3). Depend-



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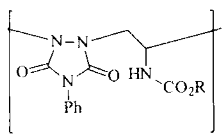

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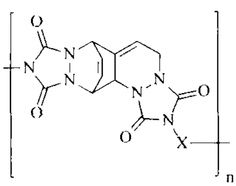

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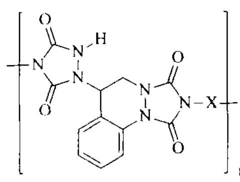

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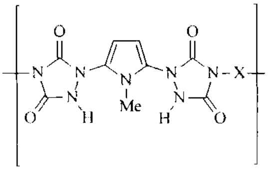

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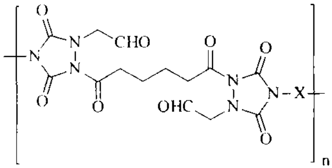
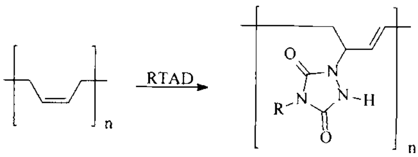


(518)

SCHEME 89



(519)

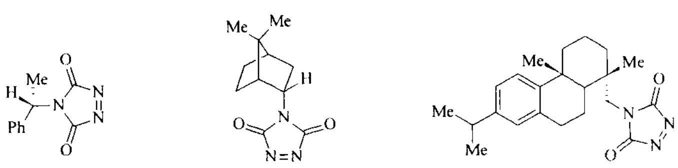
SCHEME 90

ing on the polar substituents and the substitution of the TAD, the mechanical properties of the polymers can be modified. 4-Hydroxyphenyl, 4-hydroxy-3-nitrophenyl (87CB691; 91MI2), 4-carboxyphenyl (90MMC1347; 91MMC805), and squatenyl (91MI3) TADs have been used for such modifications.

Homopolymers formed from 2,4,6-trimethoxystyrene, 4-(*N,N*-dimethylamino)styrene, and *N*-methyl-2-vinylpyrrole react with MTAD and PTAD. The reaction leads to the incorporation of the TADs into the polymers via ene reaction or electrophilic aromatic substitution (see Section IV,I). The same reaction of these polymers with bis-TADs gives cross-linked polymers insoluble in both polar and nonpolar solvents [89JPS(A)217]

4. *Use of Optically Active TADs*

Several optically active TADs, including compounds **520, 521,** and **522,** have been synthesized via the respective isocyanates and urazoles (80JA2131, 80JOC5105). Diels–Alder reaction of these optically pure TADs with some prochiral dienes has been studied. However, no meaning ful asymmetric induction has been observed under various conditions, probably because of the exceptionally high reactivity of these dienophiles. However, Diels–Alder reaction of some optically pure TADs especially (−)-endo-bornyl-TAD (**521**), with racemic chiral dienes provides mixtures of diastereomers. Such mixtures can be used directly to separate the diastereomers, or the separation can be performed in a subsequent step (79TL3597; 80JA1188, 80JA2131, 80JA5016, 80JA5026).



(520) (521) (522)

SCHEME 91

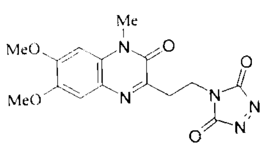
5. *Use of Triazolidinones in Analytical Chemistry*

TADs bearing highly fluorescent substituents at position 4 have been used as reagents for the determination of some biologically important compounds bearing a conjugated diene system [90JCS(CC)1416; 91MI1; 94MI1; 95YZ584; 96JCS(P1)167]. For example, DMEQ-TAD (**523**) reacts quantitatively with major vitamin D metabolites and synthetic analogues, with retinoic acid and its isomers, as well as with some other natural products containing a diene system (91TL2379; 95YZ584). 3-(Pyren-1-yl)propyl-TAD (**524**) has been recently reported to be suitable for the detection at femtomolar levels of biologically important dienes, e.g., 25-hydroxy vitamin D_3 and octadecadienoic acid, in blood serum [91MI1; 94MI1; 96JCS(P1)167].

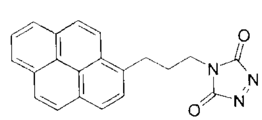
Adducts of MTAD and PTAD have been used for the identification of a conjugated diene position in aliphatic chains by mass spectroscopy (87AC1954; 90MI2). The mass spectra are characteristically simple, and the presence of abundant fragment ions indicates the position of the diene in the parent compound. The use of PTAD adducts is limited by their low volatility, but MTAD adducts are suitable for analysis by gas chromatography–mass spectroscopy (GC-MS) because of their thermal stability and sufficient volatility (90MI2). Crown ether containing TAD **525** is especially suitable for derivatization of naturally occurring dienes for electrospray ionization mass spectroscopy [93JCS(CC)664].

6. *Use of PTAD as a Mechanistic Singlet Oxygen Probe*

PTAD reacts with conjugated dienes in a Diels–Alder fashion, with mono olefins in an ene reaction to afford *N*-allylurazoles, and with some olefins to give diazetidine derivatives, products corresponding to a [2 + 2] cycloaddition reaction. Because of its similar reactivity to singlet oxygen ($^1O_2$),



(523)



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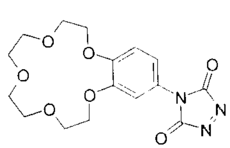

(525)

SCHEME 92

PTAD is often used to mimic mechanistically additions of singlet oxygen. The mechanistic aspects have been investigated using isotope effects (80JA6384; 90JA3607; 92JA6044), low-temperature NMR techniques (85JA5584; 90JA5364; 91JA6286; 95JOC4102), theoretical calculations, and trapping experiments (87JA6376; 88TL2769; 91TL2667; 95JOC4102). In spite of the remarkable similarity between the reactivity of singlet oxygen and PTAD, it has been shown that the mechanistic equivalence of PTAD and singlet oxygen is not as general as previously implicated (87JA6376; 88JA7167, 88JOC3129; 95JOC4102). Nevertheless, PTAD still is a useful tool.

7. *Use of PTAD as a Spin Trap*

PTAD has proved to be a particularly efficient spin trap for metal-centered radicals that do not easily add to nitroso derivatives and nitrones, the conventional spin traps. Therefore, PTAD can provide a valuable alternative to these radical scavengers (83JOC2544).

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 67

Enaminones in Heterocyclic Synthesis

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I. Introduction

Enaminones are compounds containing the system N—C=C—C=O. They are mono enamines of 1,3-diketones (vinylogous amides) or enamines of 3-keto esters (vinylogous urethanes). Their unique properties and the versatility of their applications in organic synthesis follow from the system $N_a—C_b=C_c—C_d=O_e$, which is tridentate (sites a, c, and e) toward electrophiles and bidentate (sites b and d) toward nucleophiles. This makes possible a wide variety of reactions, but with such a multiplicity of sites vulnerable to attack, reactions are sometimes unpredictable and can be unexpectedly complex.

An overview of the chemistry of enaminones was written by one of us some years ago (77CSR277). Since then many new syntheses, almost all of heterocyclic rings, have appeared. The material for this review has been assembled largely from our routine reading of the literature. Systematic [ORAC (91MI1), CAS on-line] searches were also used, but enaminones used as intermediates in synthetic schemes often do not appear in keywords or titles.

For the ring formed from the enaminone, the material has been classified in order of increasing ring size and for each ring size in order of increasing heterocycle complexity, following the conventions in the rules of nomenclature.

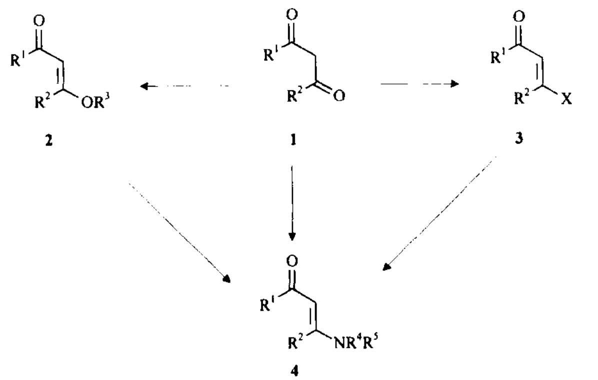
II. Preparation of Enaminones

The most important general methods for enaminone preparation are (i) direct condensations of ammonia or amines with 1,3-diketones or 3-ketoesters, (ii) nucleophilic reactions of lactams or related compounds with vinylogous acid chlorides, (iii) transformations catalyzed by organopalladium complexes, and (iv) the reactions of active methylene compounds with formamide acetals. This last method (iv) has been reviewed in detail

(79T1700) and is not covered here. Other methods of a nongeneral nature are mentioned as appropriate in the synthetic schemes.

A. Condensation of Amines with 1,3-Diketones or Their Derivatives

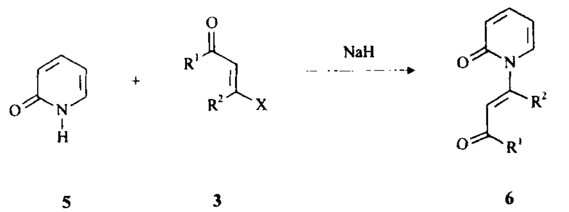
This most widely used procedure involves the condensation of ammonia or a primary or secondary amine with a dione **1** with azeotropic removal of the water (77CSR277). When this fails, as with very weakly basic amines [76JCS(P1)2207], a vinylogous ester **2** or a vinylogous acid chloride or sulfinyl derivative **3** can often be used, Scheme 1 [76JCS(P1)2211; 78TL743]. Enaminones **4** derived from low-boiling amines are sometimes prepared from the amine acetates (83S902) or Lewis acid complexes (81S880) and 1,3-diones.



R^1 = alkyl, aryl, alkoxy; R^2 = alkyl, aryl; $R^1, R^2 = (CH_2)_n$; R^3 = H, Me, Et; X = Br, Cl, sulfinyl

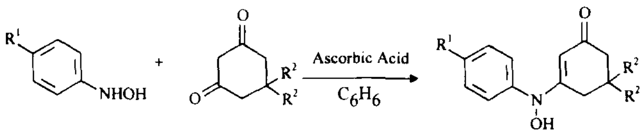
Scheme 1

In the presence of sodium hydride, 2-pyridone **5** reacts with vinylogous acid halides **3** to give enaminones **6**, Scheme 2 (78T2609).



Scheme 2

Condensation of arylhydroxylamines **7** with dimedone **8** (R^2 = CH_3) catalyzed by ascorbic acid affords good to excellent yields (52–93%) of *N*-hydroxyenaminones **9.** Yields were only 25–36% in the absence of the acid, which probably acts by suppressing the decomposition of the arlyhydroxylamines rather than by increasing the reaction rate (73TL4533).

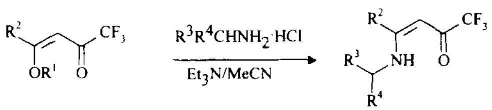


7 8 9

R^1 = alkyl, halogen; R^2 = H, Me

SCHEME 3

In the presence of triethylamine, enaminones **11** are synthesized in high yields from the corresponding amino ester or amino nitrile hydrochlorides and vinylogous esters **10,** Scheme 4 (89TL6173, 92S533). The products are precursors for trifluoromethyl-substituted pyrroles and dihydropyrroles (Section V,C).



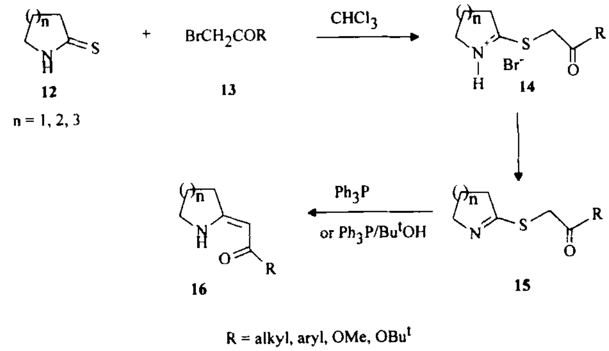
10 11

R^1 = Me, Et; R^2 = H, Me; R^3 = H, Ph, $EtSCH_2$; R^4 = CO_2Me, CO_2Et, CO_2Ph, CN

SCHEME 4

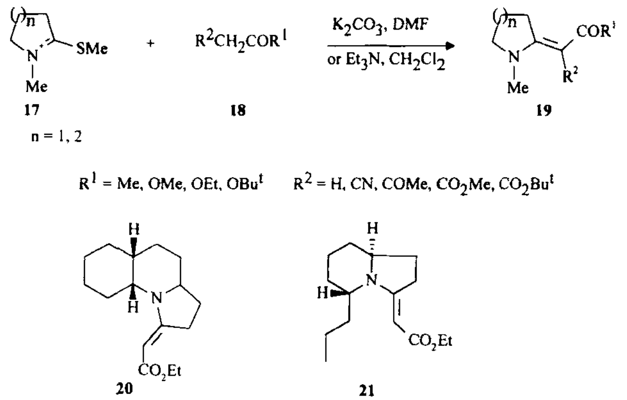
B. Reactions of Lactams and Lactims with Active Methylene Compounds and Other Nucleophiles

The elegant sulfur extrusion developed by Eschemoser and his coworkers represents a typical example of this type of reaction (71HCA710; 84JA4539). Treatment of a thiolactam **12** with a bromomethyl ketone or ester **13** gives an iminium salt **14,** which with a base gives the thioimino ester **15.** Triphenylphosphine or a triphenylphosphine/potassium *t*-butoxide mixture brings about the sulfur extrusion to give the enaminone **16,** Scheme 5. The overall yield for the three steps is usually higher than 60%, and the method is particularly useful for the preparation of cyclic enaminones, which are unstable when made in other ways. Unstable enaminones are often transformed into enaminothiones for easy isolation.



SCHEME 5

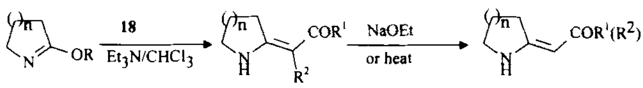
The reactions of (alkylthio)alkylideniminium salts **17** with active methylene groups **18** lead to enaminones **19** α-substituted with electron withdrawing groups, Scheme 6 (81JOC3671). Moderate to good yields are obtained in DMF with potassium carbonate or in dichloromethane with triethylamine. In some instances deacetylated products are obtained in substantial amounts with DMF/K_2CO_3, but these by-products are not seen when triethylamine is used. The enaminones **20** and **21** for use in alkaloid syntheses are prepared by this procedure from the methylthiodihydropyrrolidium salts and the magnesium salt of monoethyl malonate (81JOC3671).



SCHEME 6

Reactions of lactim ethers **22** with active methylene compounds in Et_3N/$CHCl_3$ afford enaminones **23**, generally in high yields. Thermolysis or base-catalyzed hydrolysis then leads to the enaminones **24**, Scheme 7 (79JOC3089; 81TL963; 83S195). This method is particularly useful for cyclic

enaminones, but has been applied to the preparation of acyclic enaminones from nitriles via imidates (81S130). Recently, a stereospecific preparation of **24** with exclusive Z configuration has been achieved by condensation of compounds **22** with β-ketoesters followed by decarboxylation with boric acid (86JHC1183; 90TL4873; 91CJC1201).

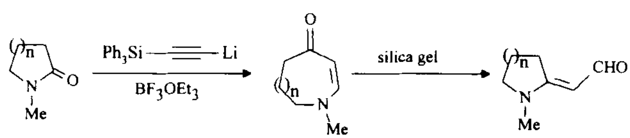


22 23 24

R^1 = Me, OMe, OEt, OBu^t R^2 = H, CN, COMe, CO_2Me, CO_2Bu^t

SCHEME 7

A reaction of lithium triphenylsilylacetylide with amides in THF unexpectedly gave enaminones in high yields (87JOC2929). An example is shown in Scheme 8, in which the cyclic amides **25** give the cyclic enaminones **26,** which on chromatography over silica gel, rearrange to the more stable enaminals **27** (87JOC2929; 88JOC2226). The triphenylsilyl group is essential for this enaminone preparation; no trialkylsilyl acetylenes reacted in the same way.

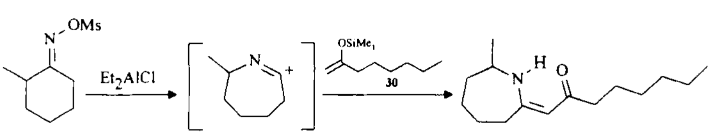


25 26 27

n = 1, 2, 3

SCHEME 8

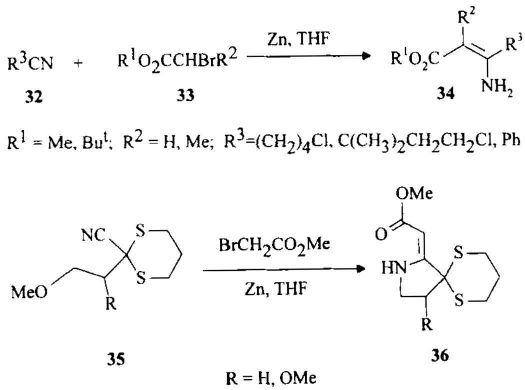
In the presence of organoaluminum reagents such as diethyl aluminum chloride (DEAC) or ethyl aluminum dichloride (EADC), oxime sulfonates rearrange in a Beckmann manner and couple with enol silyl ethers to give enaminones in moderate to good yields. In one example illustrated in Scheme 9, an interesting perhydroazepine derivative **31** was prepared in 95% yield. The generality and regiospecificity of the method have also been established (83JA6312).



28 29 31

SCHEME 9

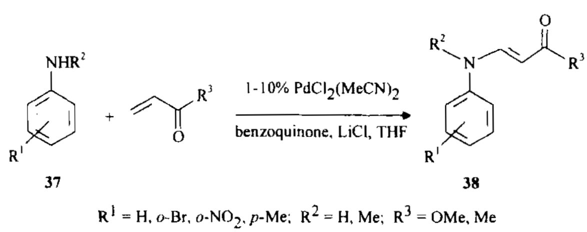
An improved Blaise reaction provides a simple access to enaminones **34**. Treatment of nitriles **32** with three to five molar equivalents of α-bromo esters **33** and activated zinc dust in refluxing THF gives the enaminones in high yield, Scheme 10. The value of the method was demonstrated by the conversion of the nitrile **35** to the pyrrolidine derivative **36**, a key intermediate in the synthesis of the alkaloid saxitonin (83JOC3833).



SCHEME 10

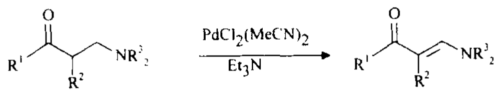
C. TRANSFORMATIONS CATALYZED BY $PdCl_2(CH_3CN)_2$

With a catalytic amount of the palladium complex $PdCl_2(CH_3CN)_2$ in the presence of benzoquinone, anilines **37** react with methyl vinyl ketone or methyl acrylate to afford the enaminones **38** in moderate to good yields, Scheme 11. The reaction is sensitive to the amine substitution; for example, benzylamine and *N*-unsubstituted anilines except *o*-bromoaniline failed to give the desired enaminones. Alkyl-substituted enones (methyl crotonate, cyclopentenone, cyclohexenone) presumably were sterically inhibited from coordination with the palladium because they also failed to undergo the reaction (81JOC2561).



SCHEME 11

The same complex in triethylamine causes dehydration of the β-amino ketones **39** to the enaminones **40** in excellent yields, Scheme 12. This method is useful because the β-amino ketones are readily available from Mannich reactions or from Michael additions of amines to enones (84CL-1419; 87BCJ3285).



39 **40**

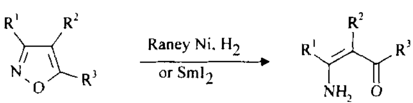
R^1 = alkyl, Ph; R^1R^2 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$[CH_2CMe_2CH_2CH_2]$-; R^3 = Me, Et

SCHEME 12

D. MISCELLANEOUS

1. *Ring-Opening of Isoxazoles*

The reductive ring-opening of isoxazoles **41** to enaminones **42** has been known for a century (1891CB3900) and has been applied to isoxazoles with a wide range of substitution patterns (50G441; 54JCS665; 66TL233; 69T389; 84TL4313). Generally, the reaction is carried out by passing hydrogen through an ethanolic solution of the substrate containing suspended Raney nickel. Substitutents such as carboxylic acids, esters, nitriles, and carbamides survive under these conditions. Samarium diiodide has been reported to catalzye the reaction efficiently by a free radical mechanism, Scheme 13 (82TL5009).



41 **42**

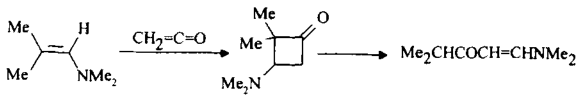
R^1, R^2, R^3 = alkyl, ester

SCHEME 13

2. *Rearrangement of Cyclobutanones*

Cycloaddition of ketene to enamines affords cyclobutanones, which upon distillation readily rearrange to enaminones (61JOC4775; 63JOC1468). For

example, enaminone **45** was obtained in 93% yield from the adduct **44** of ketene and the enamine **43,** Scheme 14. A disadvantage of the method is that a mixture of isomeric derivatives can form if the adduct has removable protons at both α positions.

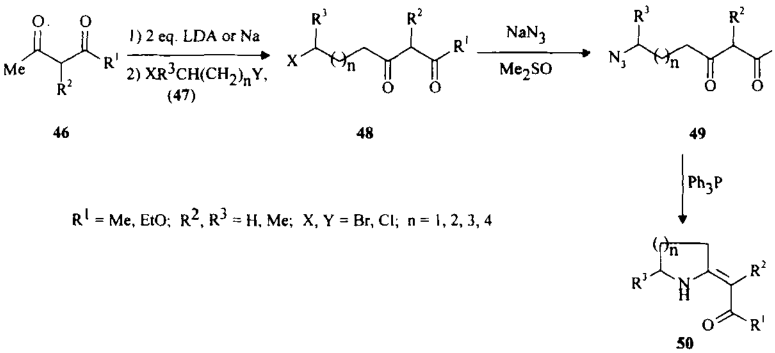


43 **44** **45**

SCHEME 14

3. *Intramolecular Aza-Wittig Reaction*

This procedure begins with monoalkylation of the dianion of **46** with an α,ω-dihaloalkane **47** to give the intermediate **48.** Displacement of the remaining halogen by sodium azide yields **49,** which is cyclized by triphenylphosphine in anhydrous ether or benzene to **50** (Staudinger reaction), Scheme 15. This complements the methods described in Section II,B and appears to be flexible with regard to ring size and to substitution pattern (85JOC5352).

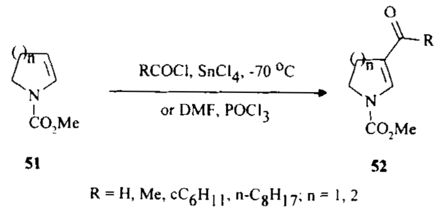


46 **48** **49** **50**

SCHEME 15

4. *Friedel–Crafts and Vilsmeier Reactions of Enecarbamates*

The Friedel–Crafts reaction of enecarbamates **51** with acid chlorides to give enaminones **52** is catalyzed by stannic chloride at low temperature, Scheme 16. The Vilsmeier reaction of **51** gives enaminals **52** (R = H) (82JA6697).

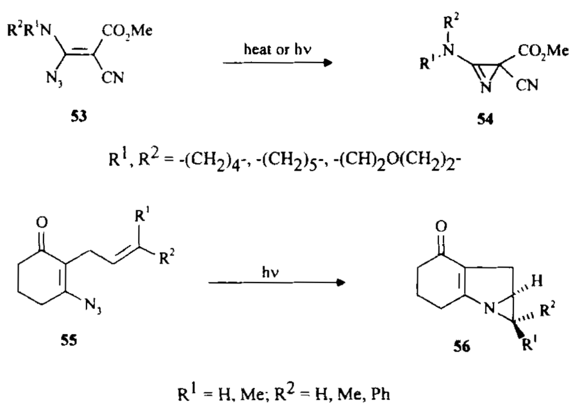


SCHEME 16

Other syntheses of enaminones with unusual structures include reduction of vinylpyridinium salts [89JCR(S)112], addition of secondary amines to acetylenic ketones [72JCS(P1)805], rearrangements of α-aminoalkylidene-β-alkoxy α-lactams (80JOC936), and nucleophilic amination of perchlorocyclobutanone (80AP959).

III. Three-Membered Rings: Azirines

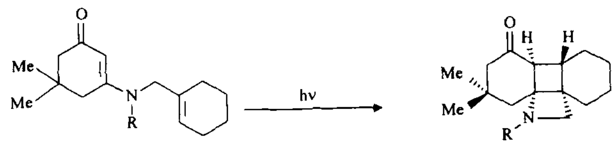
Few examples of azirine synthesis via enaminones are found in the literature, as azirines tend to undergo further reactions to give more stable compounds. One important method is the vinyl azide–olefin cycloaddition where the azides can be considered as derivatives of enaminones. The chemistry of this unique reaction has been reviewed (75AGE775). A recent example is included in Scheme 17, in which intramolecular cycloadditions of vinyl azides **53** furnish azirines **54** (87CB2003). In a similar reaction, the aziridinoindoles **56** are synthesized from **55** by insertion of the azide-derived nitrene into the olefinic bond (89H2029).



SCHEME 17

IV. Four-Membered Rings: Azetidines

Photolysis of *N*-formyl or *N*-acetyl enaminones **57** in cyclohexane produces the azetidines **58** in low yields (15%), Scheme 18 (84TL3797; 87JOC2346).

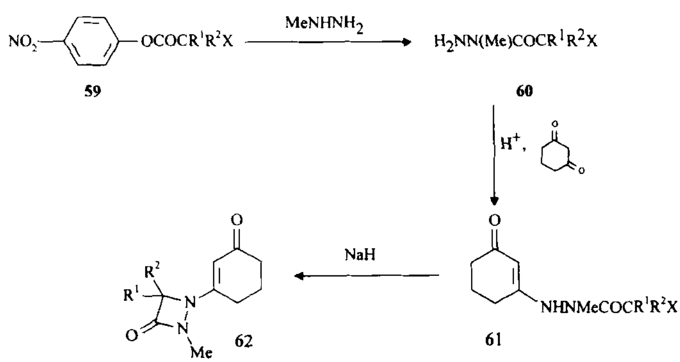


57 **58**

R = CHO, COMe

SCHEME 18

Esters **59** react with methylhydrazine to give the hydrazides **60** which, in the presence of one equivalent of acetic acid, condense with cyclohexane-1,3-dione under Dean–Stark conditions to give the enaminones **61.** Treatment of **61** with sodium hydride in tetrahydrofuran affords the diazetidinones **62** in moderate to good yields, Scheme 19 (91H2417).



R^1, R^2 = H, Me; X = Cl, Br

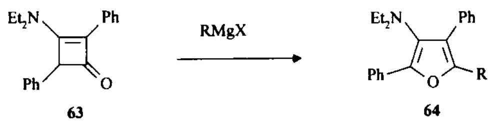
SCHEME 19

V. Five-Membered Rings

A. Furans and Furanones

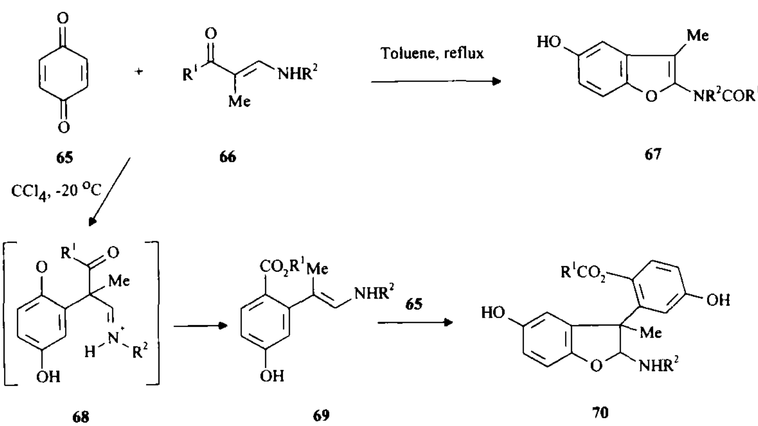
1. *Furans*

Grignard reactions of enaminone **63**, instead of giving the expected nucleophilic substitution product of the amino group, form the 3-aminofurans **64** (73TL3353). The transformation is driven by ring opening of the cyclobutanone followed by recyclization to the more stable five-membered ring. Many enaminones fail to react with Grignard reagents (77CSR277), but here the cyclobutanone ring would not allow complete electron overlap to give full mesomeric stabilization of the enaminone system.



Scheme 20

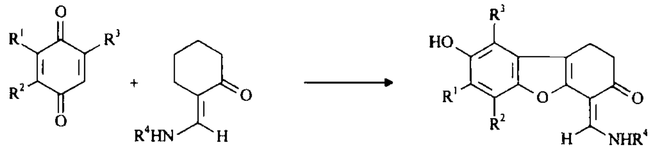
Condensations of *p*-benzoquinone **65** with acyclic enaminones **66** in refluxing toluene give benzofuran derivatives **67** (87CB1601). An earlier claim (79PJC2393) to have prepared 2*H*-1,5-benzodioxepines from this reaction turned out to be a mistake, as shown by spectroscopic data and further chemical transformations (87CB1601). However, depending on the temperature and solvent, other products can be produced by this reaction. Thus, dihydrobenzofurans **70** were formed through intermediates **68** and **69** when the reaction was carried out at $-20°C$ (82T617).



R^1 = Et, Pr^i; R^2 = Me, Et

Scheme 21

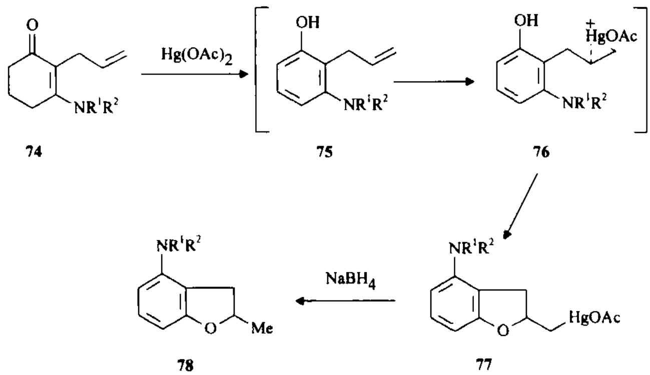
An intriguing reaction occurs between dichloro-*p*-benzoquinones **71** and 2-[(arylamino)methylene]cyclohexanones **72** to form dibenzofurans **73**, Scheme 22 (83CB152). The reaction is assumed to go via oxidation of **72** to 2-[(arylamino)methylene]-3-cyclohexenones followed by cycloaddition of **71**.



71a R^1, R^2 = Cl, R^3 = H **72** R^4 = aryl **73**
71b R^1, R^3 = Cl, R^2 = H

SCHEME 22

Dihydrobenzofurans can be synthesized via dehydrogenation–oxymercuration of 2-allyl-3-aminocyclohexenones **74**, Scheme 23 (82TL3591). Thus, enaminones **74** are dehydrogenated to the aminophenols **75** and electrophilic attack of mercury(II) at the olefinic bond then forms the intermediates **76**, which collapse to the mercurials **77**. Demercuration of **77** with $NaBH_4$ furnishes the dihydrobenzofurans **78**. If the amino group is less hindered and therefore more nucleophilic, aminomercuration occurs predominantly to give an indole (see Section V,D,3).

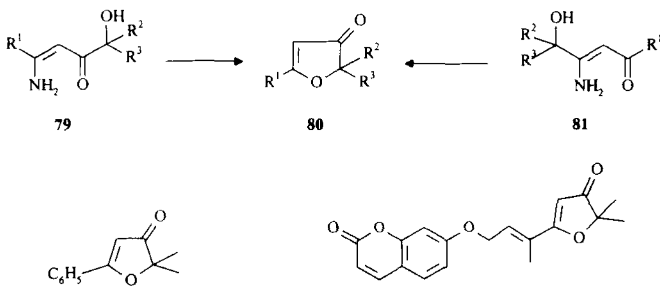


R^1 = H, R^2 = Ph, $PhCH_2$; R^1R^2 = $-(CH_2)_4-$

SCHEME 23

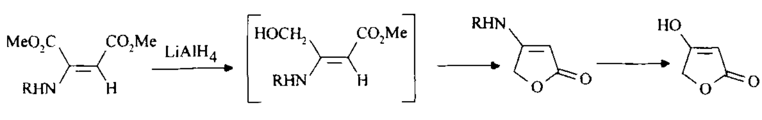
2. *Furanones*

Enaminones carrying a hydroxy group either at the α^1 position as in **79** or at the γ position as in **81** are synthetic equivalents to α-hydroxyl-1,3-diketones and are similarly capable of undergoing ring closure to give furanones **80.** The advantage of this method is that intermediates **79** and **81** are readily available through ring opening of 3,5-disubstituted isoxazoles (Section II,D,1) (66G1073, 66TL233; 67TL327; 84TL4313) and 4,5-dihydroisoxazoles (83TL2079), Scheme 24. These methods have been utilized in the synthesis of antitumor agents such as Bullatenone **82** [84JCS(P1)535; 84TL4314] and Gerparvarin **83** (85TL5319) in which a 3(2*H*)-furanone is the central structure.



SCHEME 24

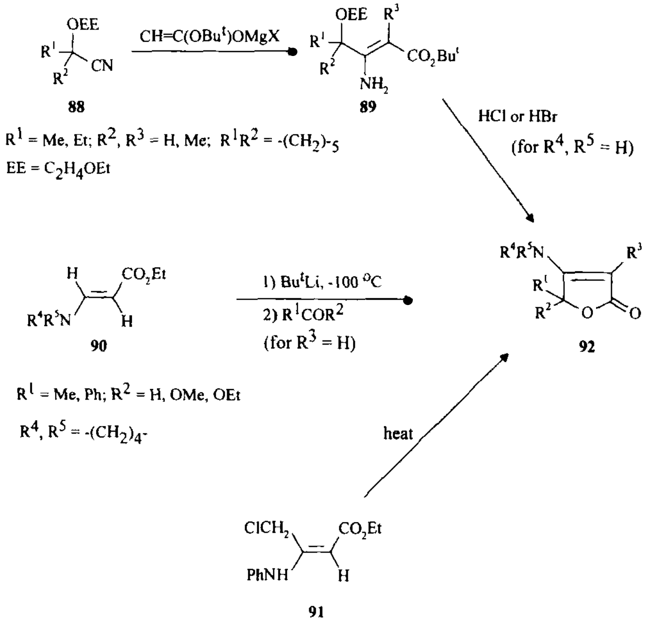
If compound **81** is a vinylogous urethane (R^1 = OR^4), the ring closure occurs readily between the hydroxy group and the ester to give 4-amino-2(5*H*)-furanones. Thus, reduction of **84** (R = Me, Bu^t, or Ph) with $LiAlH_4$ resulted in 4-aminofuranones **86,** through intermediates **85** (enaminone resonance stabilized the second ester group). Hydrolysis of **86** provided essentially pure tetronic acid **87** [75JCS(P1)588].



SCHEME 25

Several similar methods are available, including (i) reaction of *O*-protected cyanohydrins **88** with the magnesium enolate of *t*-butyl acetate followed by deprotection and cyclization of the intermediate enaminones **89**

(85TL2459), (ii) metallation of enaminones **90** followed by addition of carbonyl compounds (78AGE204), and (iii) cyclization of γ-chloro enaminones **91** (88H1907), Scheme 26. These methods provide access to a variety of substituted 4-aminofuranones.

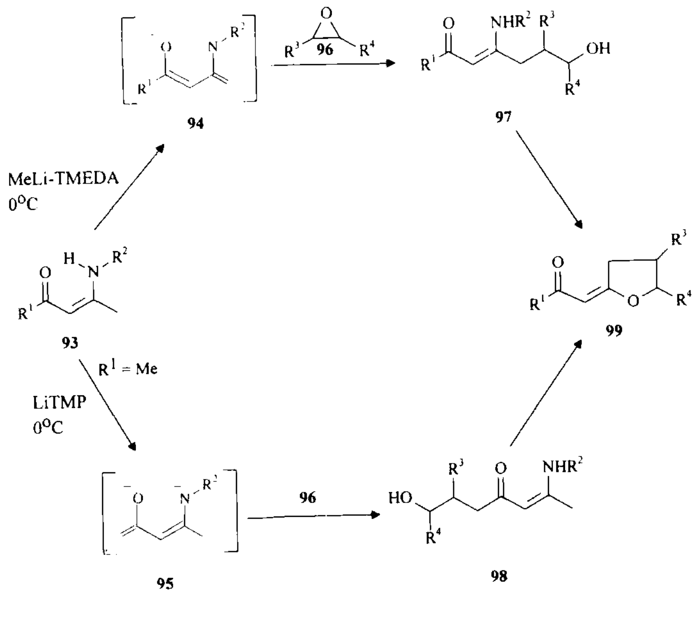


SCHEME 26

Enaminones **93** can be regioselectively dimetallated to give the kinetic dianion **94** or the thermodynamic dianion **95**. Treatment of **94** and **95** with epoxides **96** gives isomeric hydroxy enaminones **97** and **98**, which cyclize under acidic conditions to give α-tetrahydrofurylidene ketones **99** [92JCS(P1)2095]. (See Scheme 27 on facing page.)

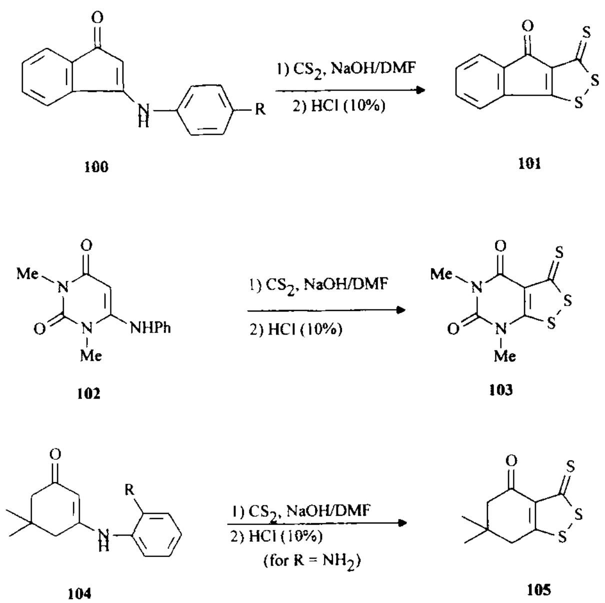
B. 3-THIOXO-1,2-DITHIOLANES

When enaminones **100** (R = H, Me) are allowed to react with carbon disulfide in NaOH/DMF followed by treatment with 10% hydrochloric acid, the dithiolane **101** is obtained. Similarly, **103** is available in 40% yield from the enaminone **102**. The enaminone **104** (R = H) derived from dimedone fails to give the corresponding dithiolane **105**; reaction is only successful when the aromatic ring carries an amino group (**104**, R = NH_2), Scheme 28 (90H1; 91JHC1245).



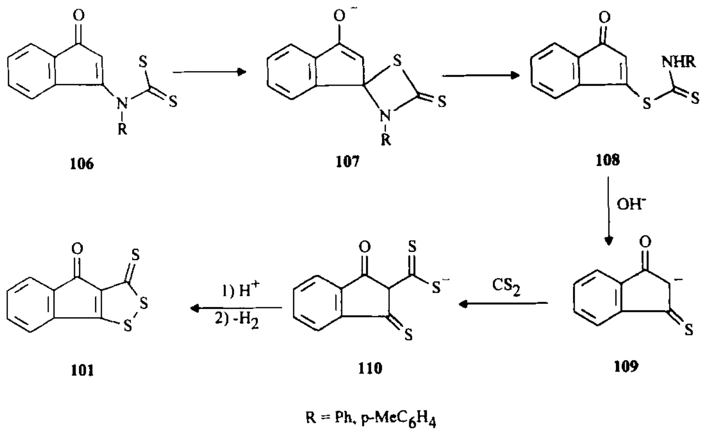
R^1 = Me, Ph; R^2 = Me, Bu; R^3 = H, Ph, Me_3Si; R^4 = H, alkyl

SCHEME 27



SCHEME 28

The mechanism for formation of **101** was assumed to begin by addition of the amino group to carbon disulfide to give **106,** followed by nucleophilic attack of the thiolate anion at C-3 and rearrangement via **107** to **108.** Hydrolysis gives the β-oxothione **109,** which reacts with a second molecule of carbon disulfide to give **110,** and oxidation completes the synthesis, Scheme 29 (90H1).



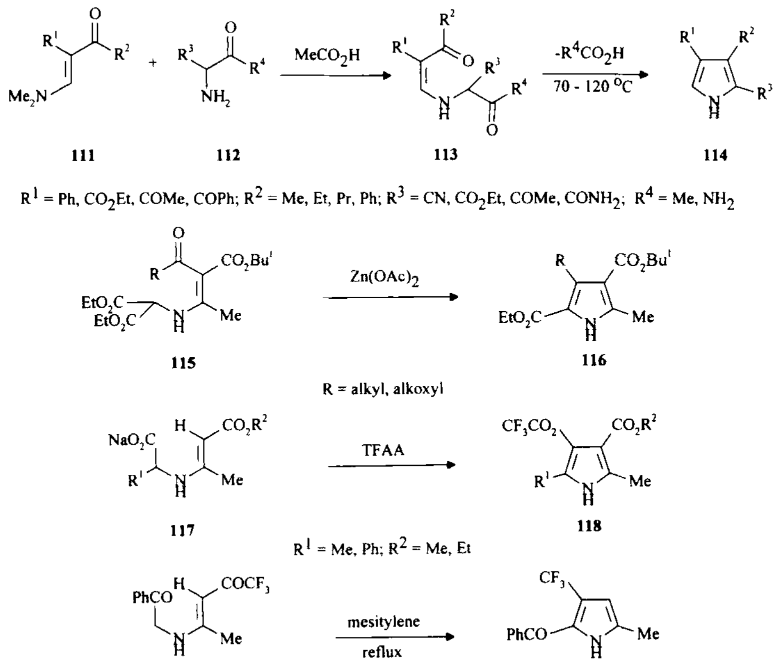
SCHEME 29

C. Pyrroles and Their Derivatives

1. *Pyrroles*

Enaminones with a carbonyl methine (RCOCH) or a nitrile methine (CNCH) group on the nitrogen readily cyclize to pyrroles. Thus, stirring an equimolecular mixture of a tertiary enaminone **111** and an α-aminocarbonyl compound **112** in acetic acid at room temperature leads to transamination to give the secondary enaminone **113,** which ring closes with elimination of acetic acid or carbamic acid to a pyrrole **114** in good yield (87S566). The cyclization of enaminones **115** (70S587) catalyzed by zinc acetate and of **117** by trifluoroacetic anhydride (75S726) gives substituted pyrroles **116** and **118,** respectively. Similarly, the ring closure of enaminone **11** at high temperature gives regiospecifically the trifluoromethyl pyrrole **119** in 92% yield, Scheme 30 (92S533). Nonfluorinated enaminones usually give mixtures of regioisomers (89H1973).

The Michael addition of phenacyl amines **120** to dimethyl acetylenedicarboxylate (DMAD) gives enaminones **121,** which cyclize under basic



111 **112** **113** **114**

R^1 = Ph, CO_2Et, COMe, COPh; R^2 = Me, Et, Pr, Ph; R^3 = CN, CO_2Et, COMe, $CONH_2$; R^4 = Me, NH_2

115 **116**

R = alkyl, alkoxyl

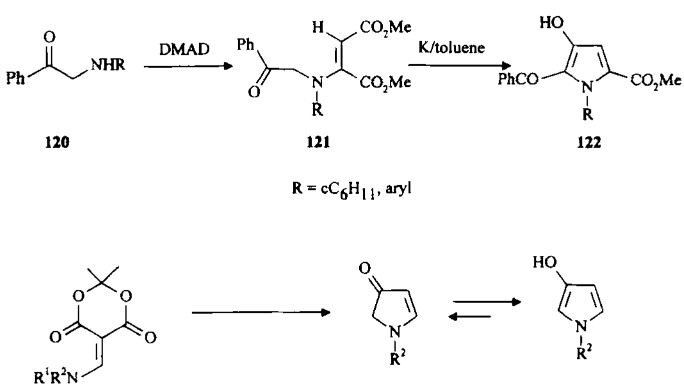
117 **118**

R^1 = Me, Ph; R^2 = Me, Et

11 **119**

SCHEME 30

conditions to 3-hydroxypyrroles **122** in 30–60% yields (68T1567; 69T527). 3-Hydroxypyrroles **124** were obtained by pyrolysis of aminomethylene Meldrum's acid derivatives **123,** Scheme 31 [85JCS(CC)213].



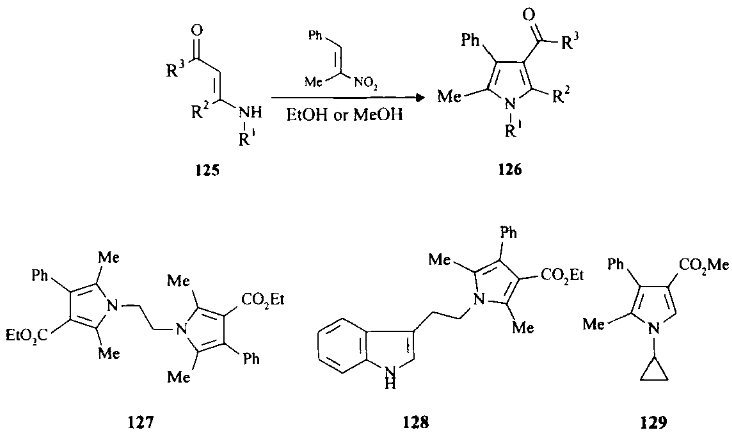
120 **121** **122**

R = cC_6H_{11}, aryl

123 **124**

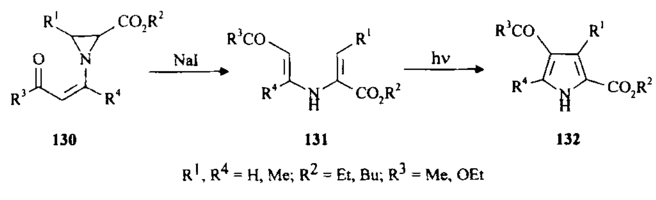
SCHEME 31

The Michael additions of enaminones to nitroalkenes (81LA1534; 87JHC23), acrylonitriles, vinyl ketones (73CPB2571; 84CPB2821), and 4-hydroxy-2-butenolide (82JOC3665) followed by cyclization provide general routes to substituted pyrroles. Scheme 32 shows that reactions of enaminones **125** with 1-phenyl-2-nitropropene give the pyrroles **126,** and the versatility of the method is demonstrated by the preparation of many structurally complex pyrroles such as **127, 128,** and **129** (81LA1534).



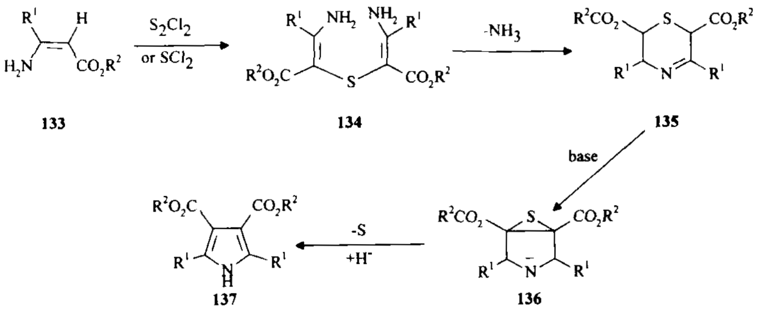
SCHEME 32

Base-catalyzed isomerization of *N*-vinylaziridines **130** followed by photolysis of the resultant *N*-vinyl enaminones **131** gives pyrroles **132,** Scheme 33 (82CJC2830; 87JOC5395). The photocyclization involves a conrotatory electrocyclic process.



SCHEME 33

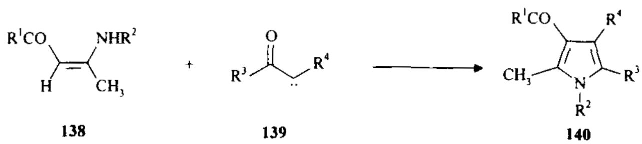
Refluxing one equivalent of S_2Cl_2 or SCl_2 with two equivalents of the amino acrylates **133** in chlorobenzene gives pyrroles **137** in good yields, Scheme 34. Initial cyclization gives the 1,4-thiazines **135** from which sulfur is extruded via **136.** This method is particularly useful for the preparation of perfluoroalkyl-substituted pyrroles, which are difficult to obtain by the Knorr synthesis (84JOC4780).



R^1 = perfluoroalkyl, Me, Ph, m-$CF_3C_6H_4$; R^2 = Me, Et

SCHEME 34

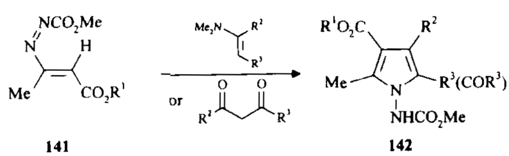
Reactions of enaminones **138** with keto carbenes **139**, generated from diazoketones in the presence of $Cu(acac)_2$, afforded the corresponding tetrasubstituted pyrroles **140** (88JOC2084). Cyclic enaminones underwent the same reaction to give tetrahydroindoles (Section V,D,4).



R^1 = Me, OEt; R^2 = H, Me; R^3, R^4 = Me, Ph

SCHEME 35

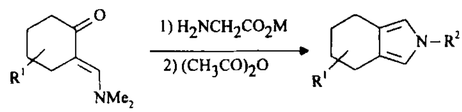
Substituted *N*-carbomethoxyaminopyrroles **142** were readily prepared in high yields from the addition of the enaminone azo derivatives **141** to enamines or β-dicarbonyl compounds, Scheme 36 (79TL2965, 79TL2969). This corrected an earlier claim to have prepared dihydropyridazines (77CL583, 77TL117) by this reaction.



R^1 = Me, Et; R^2, R^3 = alkyl

SCHEME 36

Enaminones **143,** derived from the reaction of substituted cyclohexanones with dimethylformamide dimethyl acetal, undergo [3 + 2] cycloaddition with glycinate salts followed by acetic treatment to give the *N*-acetyl pyrroles **144,** R^2 = OAc. Deacetylation affords the pyrroles **144,** R^2 = H, Scheme 37 (73IZV2572). This pyrrole synthesis proved to be general and was used in the synthesis of bi- and tricyclic ergoline dopamine agonists (80JMC481). A recent report claims that tetramethylammonium glycinate is a better reagent than the metal salts (91SC1971).

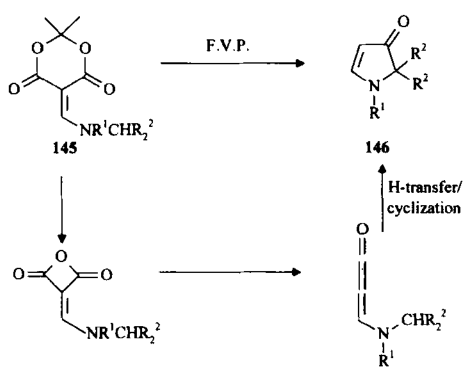


SCHEME 37

Other pyrrole syntheses include the rearrangement of 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine-4-carboxylic acids (70T4809) and oxidation of *N*-alkylaminofumarates (72JCS(CC)917; 77JCS(CC)854).

2. *Pyrrolones*

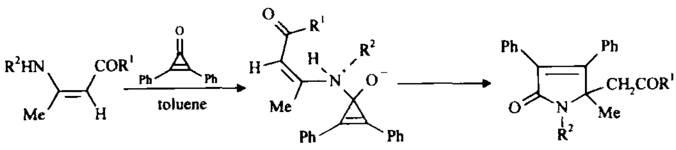
Flash vacuum pyrolysis of the enaminones **145** provides a synthesis of the pyrrolones **146,** Scheme 38 [83JCS(CC)957; 85JCS(CC)213; 86JCS(P1)-1465; 88JCS(P1)863, 88JCS(P1)869]. Detailed mechanistic work indicated that the reaction proceeds via the anhydride **147** and the methyleneketene **148** (86JCS(CC)369). From **148,** a two-step hydrogen-transfer–cyclization



SCHEME 38

mechanism was proposed based on deuterium labeling and stereochemical transfer experiments [86JCS(P1)1465; 88JCS(P1)869].

Refluxing the enaminones **149** with diphenylcyclopropenone in toluene gives first the adducts **150**, which rearrange to the pyrrolones **151** in good yields, Scheme 39. Enaminones derived from dimedone give the corresponding spiro pyrrolones, but in low yields (80JOC5340).

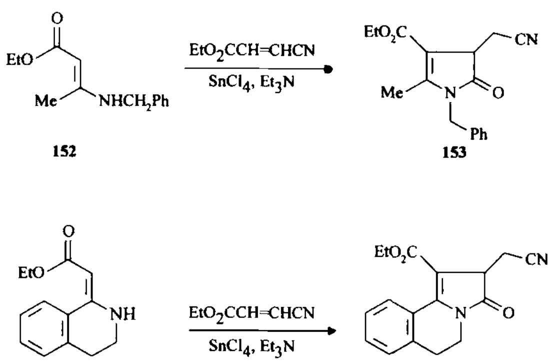


149 150 151

R^1 = Me, OEt; R^2 = H, Me

SCHEME 39

The Michael addition of enaminones **152** and **154** to ethyl 3-cyanoacrylate gives the substituted pyrrolones **153** and **155**, respectively, Scheme 40 (84CPB2821).



152 153

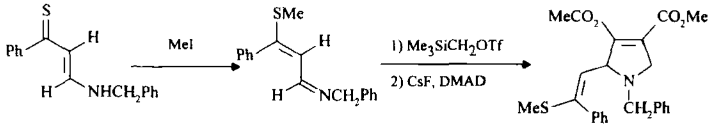
154 155

SCHEME 40

3. *Pyrrolines*

Cesium fluoride induced desilylation of immonium salts provides reactive azomethine yields, which are capable of 1,3-dipolar addition to many α, β-unsaturated compounds to form heterocycles. Examples utilizing

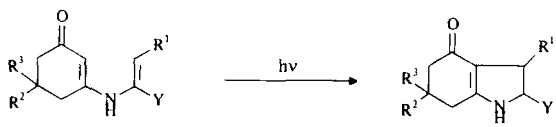
enaminone-derived immonium salts are shown in Scheme 41, where treatment of the enaminethione **156** with methyl iodide gave the intermediate **157,** which was reacted with trimethylsilylmethyl triflate followed by the cesium fluoride induced 1,3-dipolar addition with dimethyl acetylenedicarboxylate to give the pyrroline **158** in 36% yield (83TL4303).



156 **157** **158**

SCHEME 41

Photolysis of *N*-vinyl enaminones **159** derived from *N*-vinylaziridines afforded the pyrrolines **160** together with almost equal amounts of the corresponding pyrroles, Scheme 42 (87JOC5395).



159 **160**

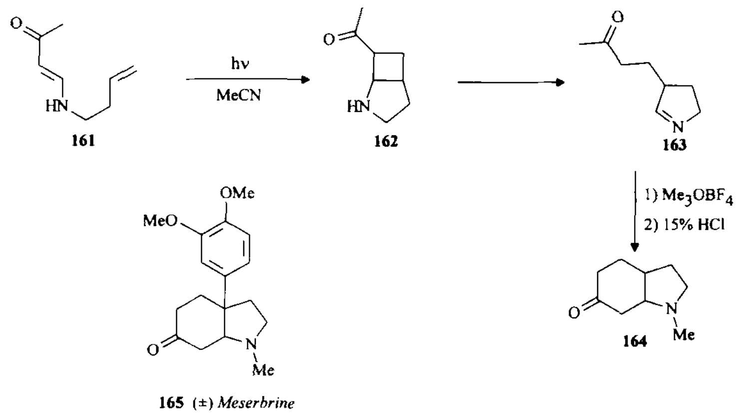
R^1 = H, alkyl; R^2, R^3 = H, Me; Y = CO_2Bu^t, CO_2Et, CN

SCHEME 42

4. *Pyrrolidines*

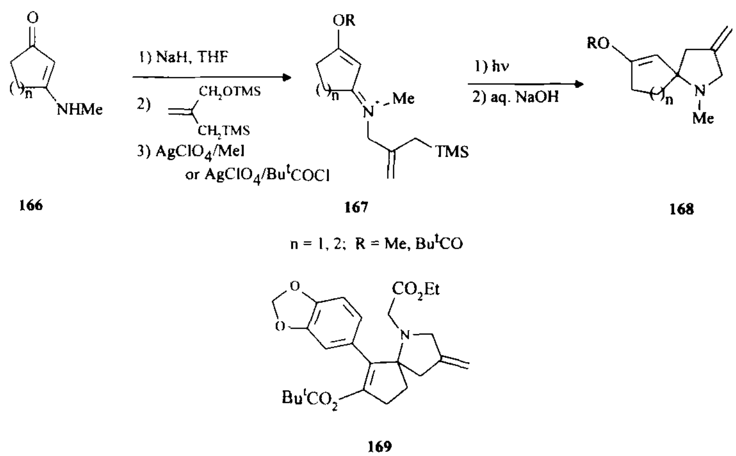
Enaminones with appropriate substitutents can be converted to pyrrolidines either by photocycloaddition or by acid-catalyzed cyclization. In Scheme 43, photolysis of the enaminone **161** gives the cyclobutanopyrrolidine **162,** which after retro-Mannich fragmentation gives the ketoimine **163.** Acid-catalyzed Mannich ring closure then furnishes the fused pyrrolidine **164** (88JA4831; 89TL5703). This method was used in the synthesis of the alkaloid (±)-Meserbrine **165** (88JA4831) and provided a second synthesis of (±)-Vindorosine **179,** which demonstrated a very high level of asymmetric induction in the intramolecular [2 + 2] photocycloaddition (90JA8971).

An approach to pyrrolidines via photocyclization of enaminone-derived allyliminium salts **167** was discovered by Mariano and co-workers (84JOC220; 84JOC228). Some allyliminium salts possess low donor-olefin



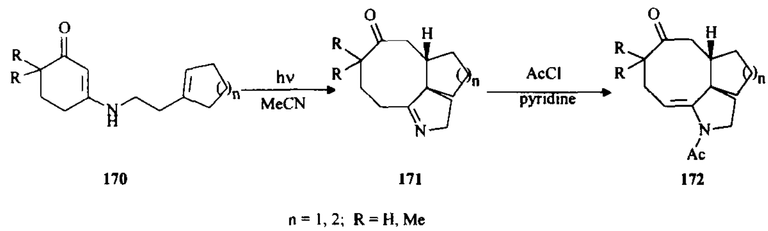
SCHEME 43

oxidation potentials ($E_{1/2}$), which allow the cyclization to compete with other modes of excited-state decay. Thus, enaminones **166** are converted into the corresponding trimethylsilylmethyl-substituted allyliminium salts **167** through *N*-allylation with $CH_2{=}C(CH_2Si(CH_3)_3)CH_2OSiMe_3$ followed by $AgClO_4$-induced methylation or pivaloylation. Irradiation of **167** and alkaline workup affords the pyrrolidines **168** in high yields, Scheme 44 (84JOC220). Allyliminium salts without the Me_3SiCH_2 substituent gave lower yields of products. This method was applied to the synthesis of structure blocks of harringtonine alkaloids such as **169** (84JOC228).



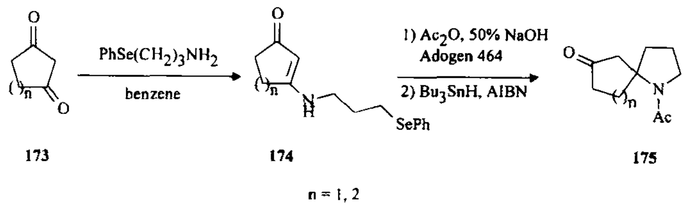
SCHEME 44

Photolysis of enaminones **170** in acetonitrile gives the pyrrolines **171**, which are acetylated to the corresponding pyrrolidines **172**, Scheme 45 (84JOC4067; 89JOC4165).



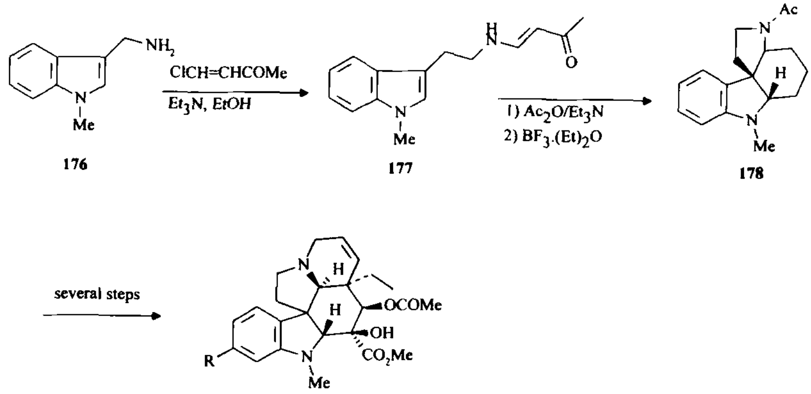
SCHEME 45

Condensation of the cyclic 1,3-diones **173** with 3-phenylselenopropylamine gives the enaminones **174**, which are acetylated under phase transfer conditions followed by radical cyclization to give pyrrolidines **175** in excellent yields, Scheme 46. Unprotected enaminones fail to undergo the cyclization, possibly because of hydrogen transfer from the NH group to the radical (89TL3865).



SCHEME 46

Early attempts to synthesize the natural alkaloids (±)-Vindorosine (71JA3299) and (±)-Vindoline (75JA6880) used a catalytic approach. Condensation of 1-methyltryptamine **176** with 1-chlorobut-1-en-3-one provided the enaminone **177**. Attempts to cyclize **177** failed until it was acetylated and then treated with boron trifluoride to give the tetracyclic indoline **178** in 35% yield. Subsequent synthetic manipulation led to the formation of (±)-Vindorosine **179a**, Scheme 47 (71JA3299). (±)-Vindoline **179b** was synthesized similarly (75JA6880).

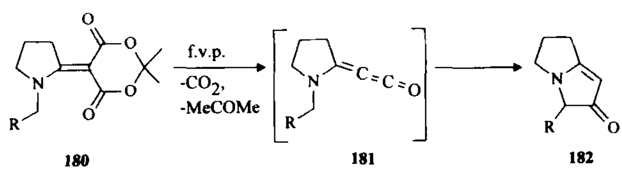


179a R = H (±)-Vindorosine;
179b R = MeO, (±)-Vindoline

SCHEME 47

5. *Pyrrolizidines*

Flash vacuum pyrolysis of Meldrum's acid derived pyrrolidine enaminones serves as a powerful tool for pyrrolidine synthesis. Thus, pyrolysis of enaminones **180** at 480 or 600°C (10^{-4}–10^{-5} torr), depending on the R group, gave the methyleneketene intermediates **181,** which cyclized to pyrrolizidines **182** in high yields, Scheme 48 (85TL833; 88JOC5680). Intermediate **181** (R = H) was the first methyleneketene to be isolated and characterized by ^{13}C NMR spectroscopy [86JCS(CC)369].

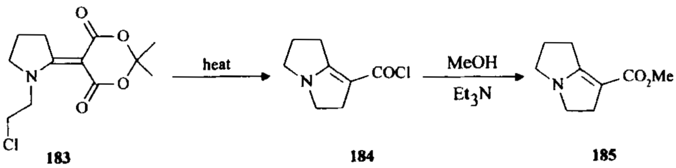


R = H, Me, Ph, CO_2Et

SCHEME 48

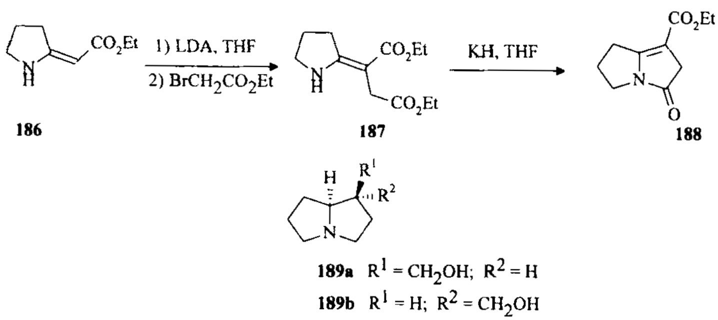
Pyrolysis of the *N*-chloroethyl-substituted enaminone **183,** however, gives the pyrrolizidine acid chloride **184,** which may be converted to the ester **185,** Scheme 49 (87TL885; 90H1251).

Pinnick and Chang reported that metalation of **186** followed by reaction with ethyl bromoacetate gave the diester **187,** which was cyclized by potas-



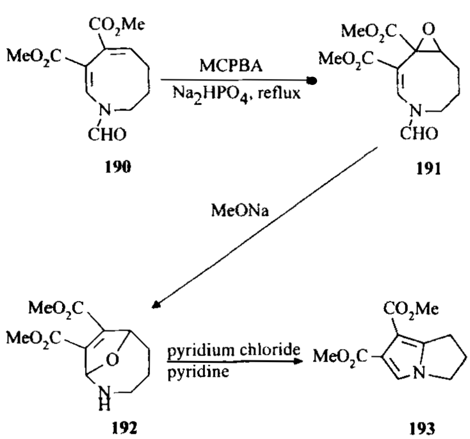
SCHEME 49

sium hydride to the lactam **188.** Compound **188** was elaborated on to Isoretronecanol **189a** and Trachelanthamidine **189b** Scheme 50 (78JOC4662).



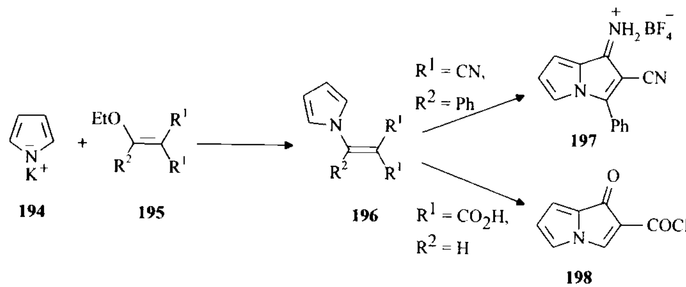
SCHEME 50

Epoxidation of the *N*-formyl enaminone **190** with *m*-chloroperbenzoic acid at high temperature gives the epoxyazocine **191.** Interestingly, deformylation of **191** generates in high yield the bicyclic amino ether **192,** which on exposure to pyridinium chloride gives the pyrrolizidine **193,** Scheme 51 (77JOC2903).



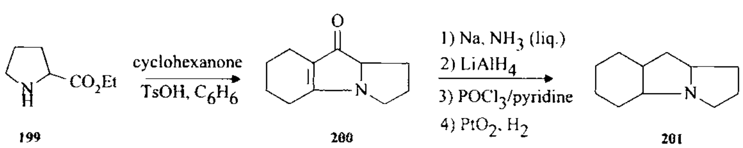
SCHEME 51

Addition of pyrrolyl potassium **194** to ethoxymethylenemalonic acid derivatives **195** gives the *N*-vinylpyrroles **196** with elimination of ethanol. Cyclization of **196** (R^1 = CN, R^2 = Ph) with the aid of tetrafluoroboric acid or aqueous hydrochloric acid gives the amino pyrrolizidine salt **197** (82CB714). Exposure of (1-pyrrolylmethylene) acid **196** (R^1 = CO_2H, R^2 = H), prepared in a different way, to phosphorus pentachloride gives the pyrrolizidine **198**, Scheme 52 (82CB706).



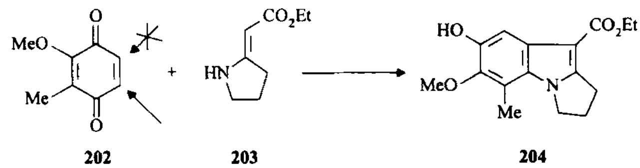
SCHEME 52

Condensation of cyclohexanone with ethyl prolinate **199** under Dean–Stark conditions gave the enaminone **200**, which was reduced in three stages to pyrrolizidine **201**, Scheme 53 (76CJC1512; 78CJC320).



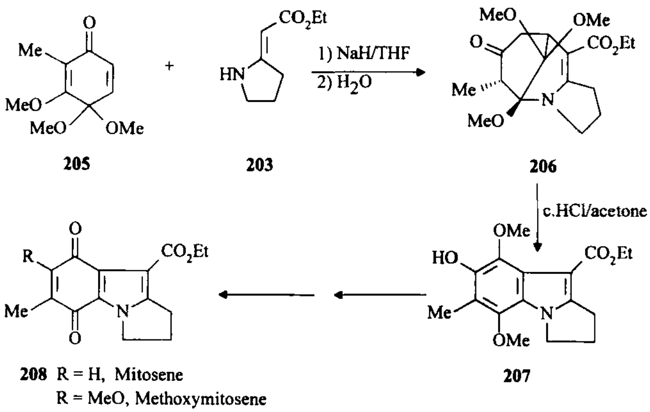
SCHEME 53

The Nenitzescu reaction, a well-known indole synthesis (Section V,D,1), is also one of the most important methods for the construction of a pyrroloindole. The reaction, which has been reviewed (73OR337), involves the condensation of a *p*-quinone with a pyrrolidine-derived enaminone. The method is valued for its application to the synthesis of many alkaloids, but regioselectivity often presents a challenging problem. For example, initial attack in the Nenitzescu reaction between 2-methoxy-3-methylquinone **202** and the vinylogous urethane **203** occurs exclusively para to the methoxy group to give **204**, Scheme 54, which is the wrong regioisomer for the synthesis of the alkaloid Mitosene **208** (82JOC4822).



SCHEME 54

Control over the regioselectivity of the previous reaction was affected by using the quinone monoketal **205,** which reacted smoothly with the sodium salt of enaminone **203,** to give the tricyclic adduct **206.** Exposure of **206** to acid resulted in rearrangement to the pyrroloindole product **207,** which was elaborated on to give Mitosene **208,** Scheme 55 (82JOC4822).



SCHEME 55

The scope of this reaction with similar five-, six-, and seven-membered ring-based enaminones was investigated and the corresponding products were obtained in 59 to 84% yields (82JOC4822), Table I. Reactions of enaminones with dibromoquinone or 2-bromonaphthoquinone also gave pyrroloindoles (83JA2859; 92TL531).

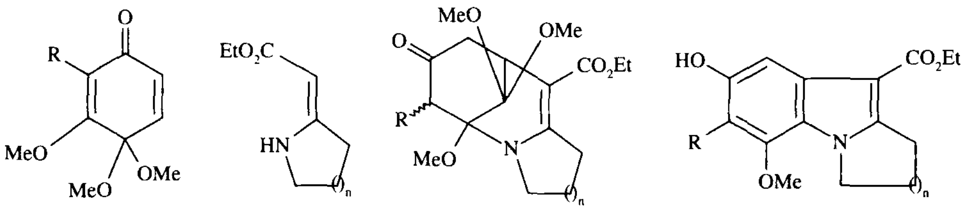
D. Indoles and Carbazoles

1. *The Nenitzescu Reaction*

Since its discovery 60 years ago (29MI1) the Nenitzescu reaction has been one of the most general methods for indole, or more precisely 5-

TABLE I

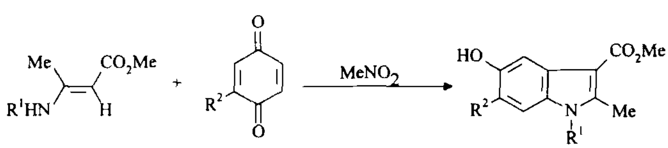
PREPARATION OF PYRROLIZIDINES[a]



R	n	Tricyclic adduct (%)	Annelated indole (%)
H	1	87	89
H	1	74	96
Me	1	87	94
H	2	85	99
Me	2	—	59
H	3	75	89
Me	3	—	64

[a] Ref. 82JOC4822.

hydroxyindole, synthesis. The reaction usually involves the condensation of a *p*-quinone with an enaminone. A wide-ranging review appeared in 1973 (73OR337), but improvements in yields, extension of the scope of the reaction, and details of the mechanism continue to be announced. Thus, it was discovered that the yields can be dramatically increased by employing nitromethane as the solvent and by using the methyl esters **209** as substrates instead of ethyl esters, Scheme 56 (79TL4009). In this particular series, the yield went down as the size of either the alkyl moiety of the enaminone (R^1) or the 2-substituent (R^2) increased. A bimolecular face-to-face electron transfer complex was proposed as a key intermediate in the reaction mechanism (79TL4009). The generally accepted classical mechanism involves a stepwise unimolecular internal oxidation–reduction pathway (73OR337).

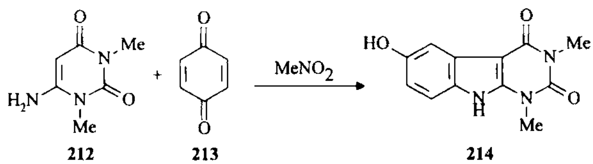


209 **210** **211**

R^1 = H, Ph, alkyl; R^2 = H, Me

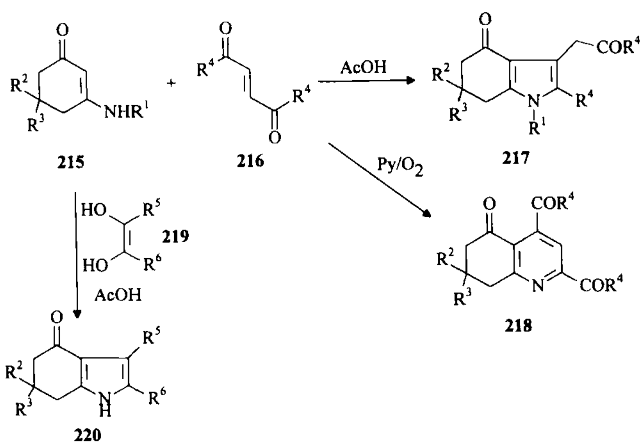
SCHEME 56

The extension of the Nenitzescu reaction to 1,3-dimethyl-6-aminouracil **212** gave the pyrimido[4,5-b]indole **214** in a much better yield in nitromethane (41%) than in the conventional acetic acid (8%), Scheme 57 (81JOC4197).



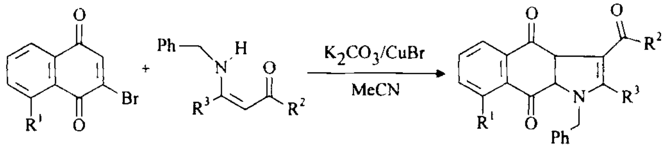
SCHEME 57

The Nenitzescu reaction of 3-aminocyclohex-2-enones **215** with diacylethylenes **216** gave dihydroindolones **217** under acidic conditions, but dihydroquinolones **218** under dehydrogenation conditions. 1,3-Dimethyl-6-aminouracil reacts similarly (74H645; 75H183; 76CPB1160). Condensation of **215,** R^1 = H, R^2, R^3 = H, CH_3, with α-diketols **219** gave the dihydroindolones **220** (71AP73).



SCHEME 58

The reactions of 2-bromonaphthoquinone (**221,** R^1 = H) and 3-bromojuglone (**221,** R^1 = OH) with enaminones **222** gave regioselectively benzo[*f*]indoles or tetrahydrobenzo[*h*]carbazoles **223,** Scheme 59. This modification of the Nenitzescu reaction opened up new entries to the Kinamycin alkaloid framework (92TL535).



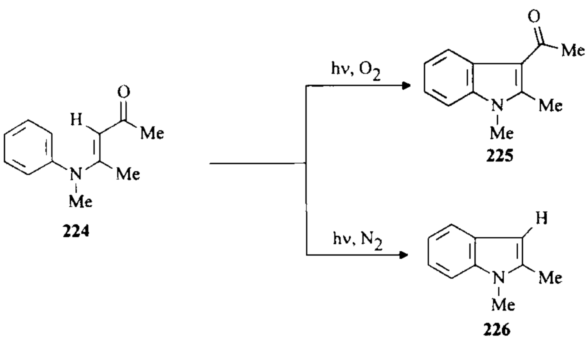
221 222 223

R^1 = H, OH; R^2, R^3 = H, Me, -$(CH_2)_3$-, -$CH_2CMe_2CH_2$-

SCHEME 59

2. *Photocyclization*

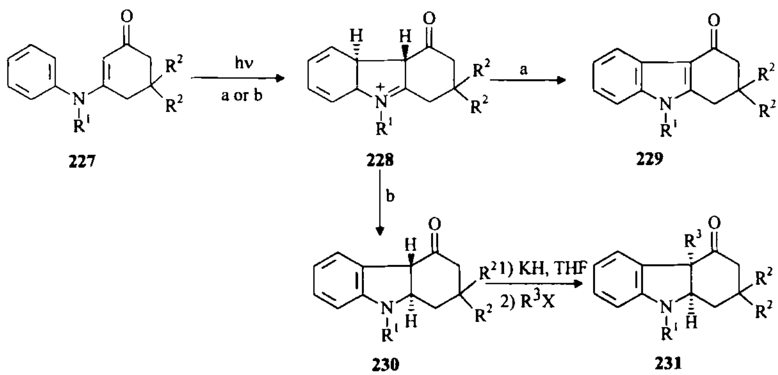
The photocyclization of *N*-aryl enaminones is a valuable indole or carbazole synthesis because *N*-aryl enaminones are easily available, photolysis conditions are mild, and yields of products are generally high. Irradiation of 4-(*N*-methylanilino)pent-3-en-2-one **224** gives the expected photo product **225** under aerobic conditions, but under nitrogen, 1,2-dimethylindole **226** is obtained. Two consecutive 1,2-hydrogen shifts followed by the loss of acetaldehyde were suggested to explain the formation of **226,** Scheme 60 (80TL3969; 85TL143).



SCHEME 60

Irradiation of the tertiary aryl enaminones **227** in ether under nitrogen gives, via a conrotatory ring closure, the dipolar intermediates **228.** A trace of oxygen present oxidizes **228** to dihydrocarbazol-4(5*H*)-ones **229.** In carefully deoxygenated benzene, however, **228** undergoes thermal, suprafacial [1,4] sigmatropic hydrogen shifts to give *trans*-tetrahydrocarbazol-4(5*H*)-ones **230** (72TL2513; 73BCJ2504; 88JHC201). Treatment of **230** with

potassium hydride in THF followed by quenching with electrophiles gives the more stable, substituted *cis* isomers **231,** Scheme 61 (88JHC201).

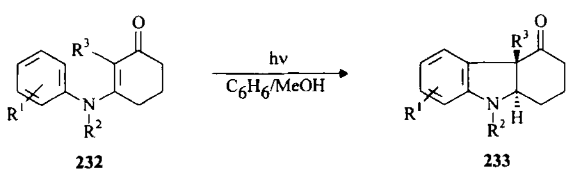


a: ether; b: benzene or benzene/methanol

R^1 = Me, MeC_6H_4, p-$MeOC_6H_4CH_2$; R^2 = H, Me; R^3 = alkyl

SCHEME 61

Similarly, direct photolysis of enaminones **232** resulted in the formation of *trans*-**233** in very high yields, Scheme 62 (85TL2323; 89CJC213). Photolysis of bromo-substituted aryl enaminones also afforded high yields of dihydrocarbazol-4(5*H*)-ones [87JCS(CC)766].

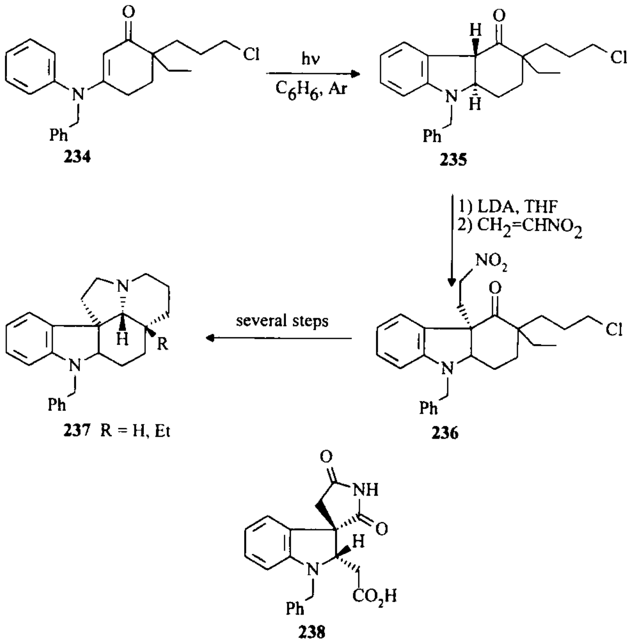


R^1 = 5,6,7 or 8-MeO; R^2 = H, Me, $PhCH_2$; R^3 = Me, CH_2=$CHCH_2$

SCHEME 62

These methods have proved useful in the synthesis of indole alkaloids. For example, (±)-*N*-benzyl aspidospermidine **237** (R = Et) was prepared via photocyclization of enaminone **234** to **235** followed by alkylation with nitroethene to **236,** which was elaborated on to the alkaloid,

Scheme 63 (92TL4001). *N*-Benzyldeethylaspidospermidine (**237**, R = H) (85JOC5517) and the spiroindole **238** (91TL6129), a precursor of the Aspidosperma alkaloids, were prepared by similar strategies.



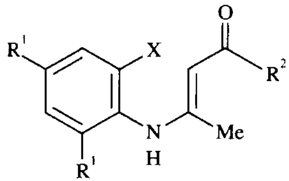
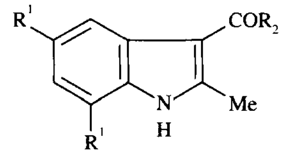
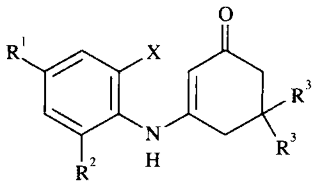
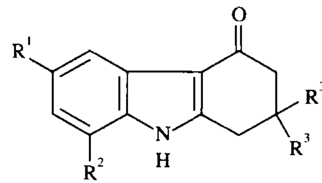
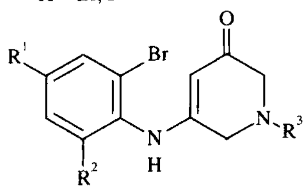
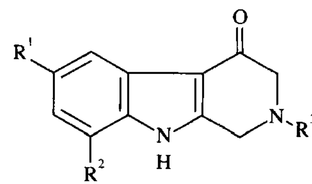
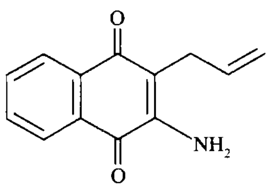
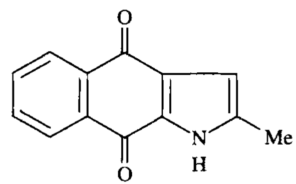
SCHEME 63

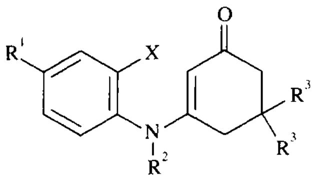
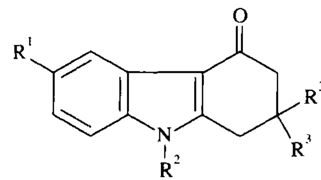
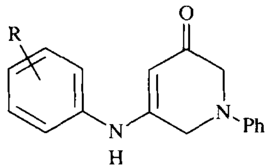
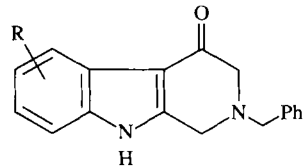
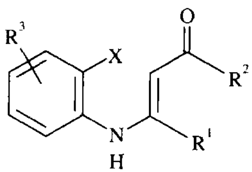
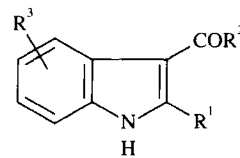
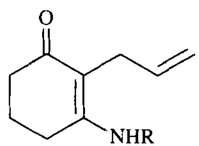
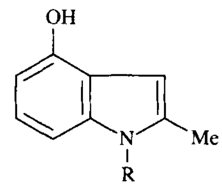
3. *Metal-Catalyzed Cyclization*

Indoles and carbazoles are also prepared by cyclization of *N*-2-haloaryl or *N*-aryl enaminones, catalyzed by copper salts or palladium complexes. The copper-catalyzed cyclization generally involves treatment of the enaminones with NaH in HMPA followed by heating with 1.5–2.0 equivalents of copper(I) iodide. The reaction efficiency depends largely on the reactivity of the halogen—bromo- and iodo-substituted enaminones give high yields of products, whereas chloro substituted enaminones give low yields (82CL2031; 91H2399) (Table II, entries 1 and 2). Piperidine-3,5-dione derived enaminones undergo similar smooth cyclization to give

TABLE II

PREPARATION OF INDOLES AND CARBAZOLES BY METAL-CATALYZED CYCLIZATIONS

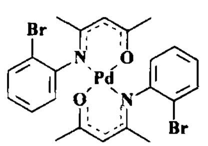
Entry	Enaminone	Reagent	Product	Reference
1	 X = Br, I	(1) NaH (2) CuI, HMPA		91H2399
2	 X = Br, I	(1) NaH (2) CuI, HMPA		82CL2031
3		(1) NaH (2) CuI, HMPA		84S616
4		(1) $PdCl_2(MeCN)_2$ (2) Et_3N		78JOC5800

5	 X = Br, I, H	$Pd(OAc)_2$ or $Pd(OAc)_2/PPh_3$		80JOC2938
6		$Pd(OAc)_2$		90H911
7	 X = Br, H	$Pd(OAc)_2/P(C_6H_4CH_3\text{-}o)_3$ Et_3N/DMF Sealed tube		86BCJ927 90S215
8		(1) $Hg(OAc)_2$ (2) $NaBH_4/NaOH$		82TL3591

1,2,3,4-tetrahydro-4-oxo-β-carbolines in good yields (91H2399) (Table II, entry 3). The yields are much better than those catalyzed by the palladium complex. A one-pot synthesis of 2,3-disubstituted indoles by reaction of enolates with 2-iodoaniline catalyzed by copper iodide probably proceeds through enaminone intermediates (84S616).

Other enaminones undergo smooth palladium-catalyzed cyclization to give indoles and carbazoles. 2-(2-Propenyl)-3-aminonaphthoquinone is cyclized in the presence of stoichiometric amounts of $PdCl_2(CH_3CN)_2$ and Et_3N to give 2-methylbenzo[*f*]indole-4,9-dione in a 30% yield (78JOC-5800) (Table II, entry 4). Treatment of *N*-2-haloaryl enaminones with catalytic amounts of $Pd(OAc)_2(PPh_3)_2$ in DMF/$NaHCO_3$ give carbazoles. Nonhalogen-substituted enaminones give similar products using stoichiometric proportions of $Pd(OAc)_2$ (80JOC2938) (Table II, entry 5). Some carbolines are also prepared like this (90H911) (Table II, entry 6). The cyclization usually gives low yields and lacks regioselectivity when there is a meta substituent on the aniline ring. But a methoxy group at the meta position increases the yield substantially, indicating that the reaction involves electrophilic palladination (80JOC2938; 90H911).

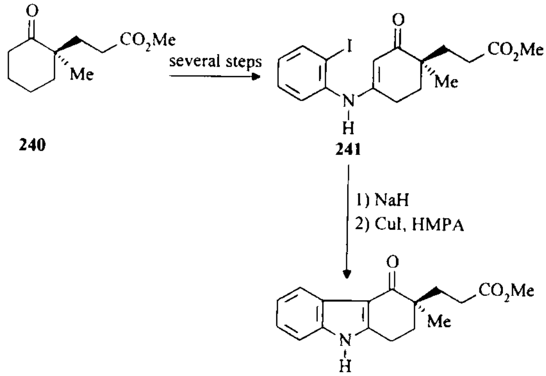
Much better yields are reported for reactions carried out in sealed tubes (86BCJ927; 90S1215) (Table II, entry 7). The choice of base and solvent, however, can dramatically affect the outcome of the reaction. Thus, when the enaminone (Table II, entry 7, X = Br, $R^1 = R^2 =$ Me, $R^3 =$ H) was treated with $Pd(OAc)_2/PPh_3$ in the presence of $NaHCO_3$ in DMF, a palladium complex **239** was obtained in 48% yield without any trace of the desired indole [81JCS(D)2212; 90S215].



239

The dehydrogenation–aminomercuration of enaminones also affords good yields of indoles (82TL3591) (Table II, entry 8). The mechanism of this reaction is similar to that of the formation of dihydrobenzofurans (Scheme 23), but with the amino group as the nucleophile.

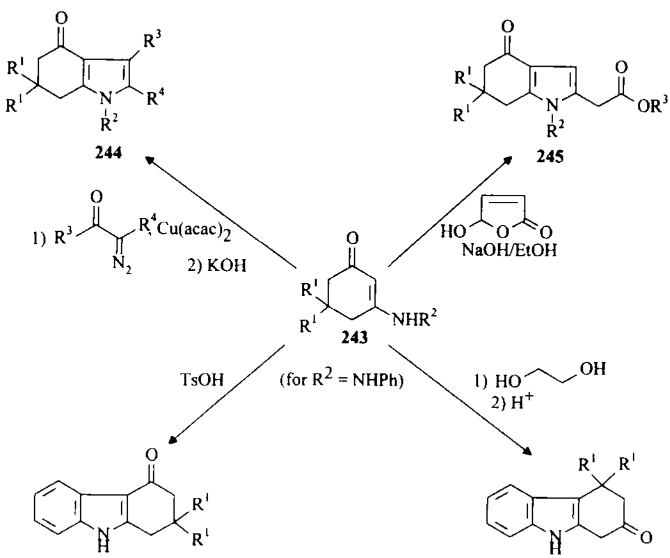
The synthetic utility of copper-catalyzed cyclizations has been well demonstrated in the synthesis of alkaloids. For example, the enaminone **241**, prepared for the (*R*)-keto ester **240** through multiple steps, gave the carbazolone **242**, Scheme 64, which was elaborated further to Aspidosperma alkaloid analogues (90TL879, 90TL883).



SCHEME 64

4. *Miscellaneous*

Reactions of enaminones **243** with keto carbenes give tetrahydroindoles **244.** Open-chain adducts are formed in R^2 is hydrogen, but can be converted to **244** by potassium hydroxide in ethanol, Scheme 65 (88JOC2084).

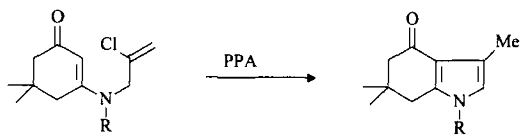


SCHEME 65

Base-catalyzed reactions of the enaminones **243** with 4-hydroxy-2-butenolide give tetrahydroindole-2-acetic acids **245** (R^3 = H) [or the methyl esters (R^3 = Me) by *in situ* treatment with diazomethane], Scheme 65 (82JOC3665).

The Fisher indole synthesis with enaminones derived from hydrazines offers a facile approach to carbazoles. 4-Oxo-tetrahydrocarbazoles **246** are the sole products when enaminones **243** (R^2 = NHPh) are refluxed with *p*-toluenesulfonic acid in toluene, but 2-oxo-tetrahydrocarbazoles **247** are obtained as the major products when **243** (R^2 = NHPh) are treated with ethylene glycol followed by hydrolysis of the resulting ketal (73JOC2729). Similar ring closures with cyclohexanone are reported to give octahydrocarbazole-4-ones, which may be dehydrogenated with chloranil to the corresponding tetrahydrocarbazoles (70CB1767; 73CB745).

N-(2-Chloroallyl)-enaminones **248** undergo electrophilic cyclization upon treatment with polyphosphoric acid (PPA) to give 3-methyl tetrahydroindol-4-ones **249** in good yields, Scheme 66 [75JCS(P1)1446].

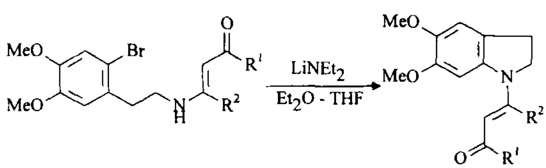


248 **249**

R = Et, Ph, p-ClC_6H_4

SCHEME 66

Treatment of the bromoenaminones **250** with lithium diethylamide in ether–THF causes intramolecular cyclization to give the dihydroindoles **251**, Scheme 67. Benzyne derivatives were assumed to be the reactive intermediates (78TL3817).

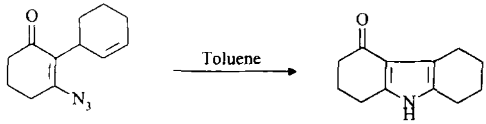


250 **251**

R^1R^2 = -$CH_2CMe_2CH_2$-,

SCHEME 67

Thermolysis of the azide **252** in toluene gives the octahydrocarbazole **253** in 67% yield, Scheme 68 (89H2029). This reaction is exceptional; usually thermolyses of this type of enaminone give aziridinoindoles as the major products (Section III).

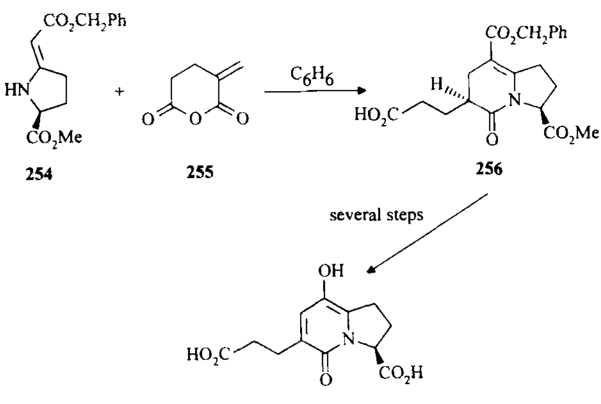


252 **253**

SCHEME 68

E. INDOLIZIDINES

Pyrrolidine-derived enaminones such as **254** are useful in the construction of indolizidines, which are the core structures of some alkaloids. Condensation of **254** with α-methyleneglutaric anhydride **255** in refluxing benzene produced the hexahydroindolizidine **256**, which was elaborated on to the angiotensin-converting enzyme (ACE) inhibitor A58365A **257**, Scheme 69 (89TL3621, 89TL3625).

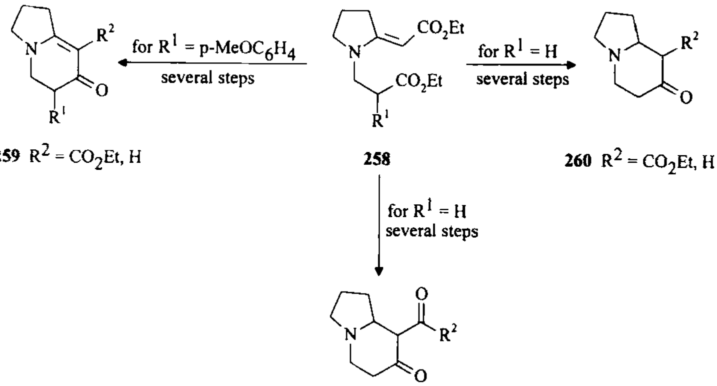


254 **255** **256**

257 A58365A

SCHEME 69

Enaminones **258**, prepared by the Eschemoser method (Section II,B), were converted by different procedures to the indolizidines **259**, **260**, and **261**, Scheme 70 (80JOC1713, 80TL1373). These indolizidines are potential precursors of the Elaeocarpus alkaloids and **259** (R^1 = p-$CH_3OC_6H_4$) eventually led to the synthesis of Ipalbidine (80JOC1713).

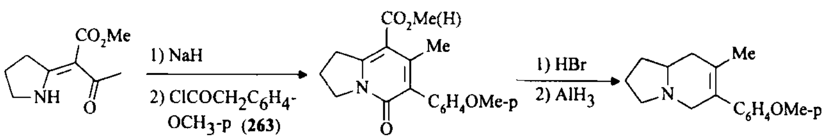


259 $R^2 = CO_2Et$, H **258** **260** $R^2 = CO_2Et$, H

261 R^2 = Pr, 2-Me,6-MeOC$_6$H$_3$

SCHEME 70

A slightly different synthesis was used for preparation of Ipalbidine and Ipalbine from the enaminone **262,** which was acylated with the acid chloride **263** and cyclized in base. The resulting pyridone **264** was hydrolyzed and decarboxylated followed by reduction to give the racemic Ipalbidine **265,** Scheme 71. Resolution of **265** and further chemical transformations led to Ipalbine (71HCA513).

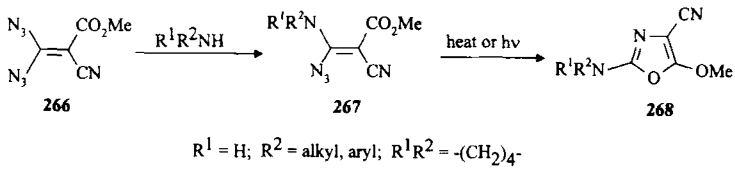


262 **264** **265**

SCHEME 71

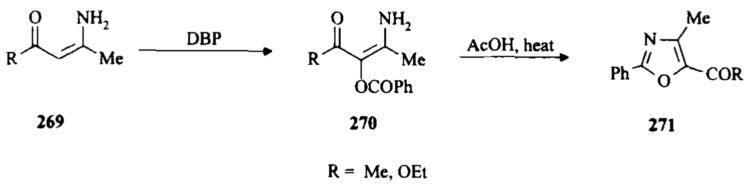
F. OXAZOLES AND OXAZOLIDINONES

The synthesis of oxazoles via thermolysis or photolysis of β-azido or β,β-diazido ketones, esters, or nitriles, which can be considered as enaminone derivatives, is well known and has been reviewed in detail (75AGE775). A recent example is the reaction of methyl 3,3-diazido-2-cyanoacrylate **266** with amines to give enaminones **267,** which undergo thermolysis or photolysis to give, probably via azirine intermediates, the oxazoles **268** in good yields, Scheme 72 (90CB115).



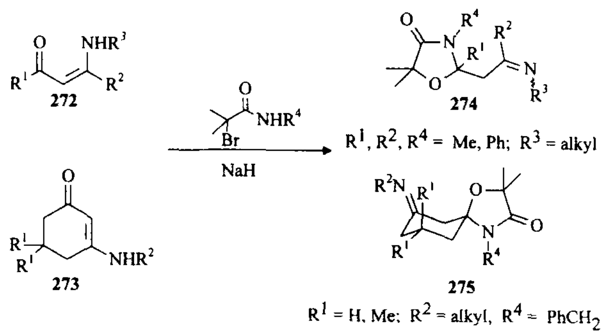
SCHEME 72

The acyclic enaminones **269** give, with dibenzoylperoxide (DBP), α-benzoyl derivatives **270,** which are converted to oxazoles **271** in refluxing acetic acid, Scheme 73 (65AK519).



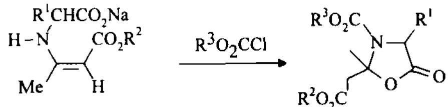
SCHEME 73

The reaction of enaminones **272** and **273** with 2-bromo-2-methylpropanamides is promoted by sodium hydride to afford the oxazolidin-4-ones **274** and spiro-oxazolidin-4-ones **275,** Scheme 74. Imines **275** could hydrolyzed to the corresponding ketones [84JCS(P1)781].



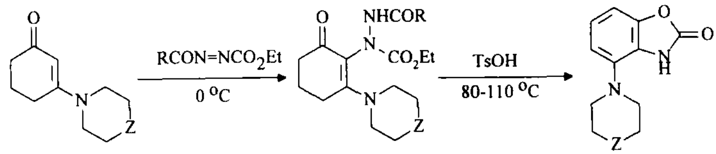
SCHEME 74

Oxazolidin-5-ones **277** are prepared from the enaminones **276** and alkyl chloroformates, Scheme 75 (75S724). The reactions of enaminones **278** with diimides give adducts **279,** which are aromatized and subsequently converted to benzoxazol-2(3*H*)-ones **280,** Scheme 76 (83JHC305).



276 277

SCHEME 75



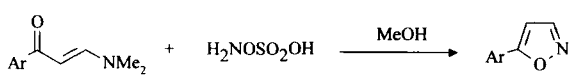
278 279 280

R = OEt, Ph, p-$NO_2C_6H_4$; Z = O, CH_2

SCHEME 76

G. ISOXAZOLES

The reactions of acyclic enaminones with hydroxylamine give, in general, good yields of isoxazoles (54IZV47; 63AHC365; 74JHC275; 77JHC345). An example shown in Scheme 77 is a convenient preparation of the 5-substituted isoxazoles **283** from the enaminones **281** and hydroxylamine-*O*-sulfonic acid **282** (80JOC4857). Some enaminones with hydroxylamine under acidic conditions were reported to give benzopyranoisoxazoles (86JHC1753).

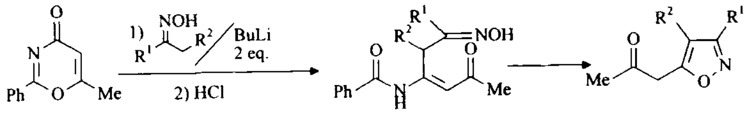


281 282 283

Ar = aryl

SCHEME 77

Nucleophilic attack by an oxime dianion on the oxazinone **284** gives an enaminone intermediate **285,** which spontaneously cyclizes to an isoxazole **286,** Scheme 78 (89H1443). In some cases, depending on the oxime substituents, pyridine *N*-oxides are the sole products (Section VI,B,3).

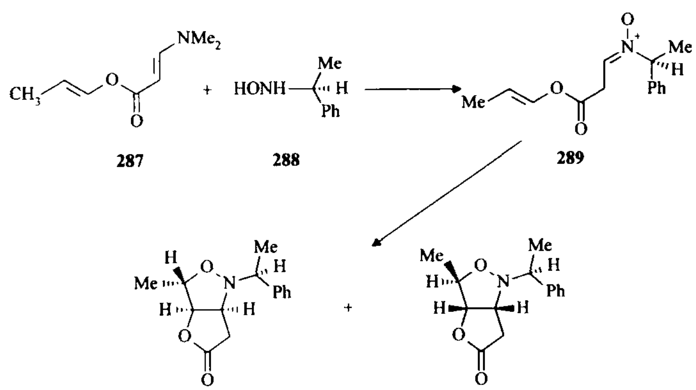


284 285 286

R^1 = Me, Ph; R^2 = H; R^1R^2 = -$(CH_2)_5$-, -$(CH_2)_6$-

SCHEME 78

Treatment of enaminone **287** with the oxalate salt of the hydroxylamine **288** in refluxing xylene generates the nitrone **289** with elimination of dimethylamine. Without isolation, the nitrone undergoes intramolecular cycloaddition to give in 68% yield an 82 : 18 mixture of diasteroisomeric furoisoxazolines **290a** and **290b,** Scheme 79. The furoisoxazoline **290a** was used in a chiral synthesis of L-acosamine and L-daunosamine (81JA3956).

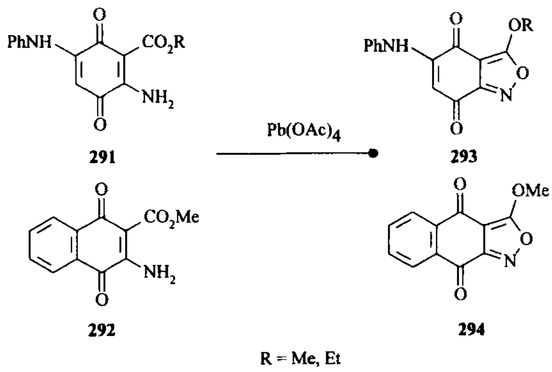


287 288 289

290a 290b

SCHEME 79

Oxidative cyclization of quinone-derived enaminones with lead tetraacetate gives access to the isoxazoloquinones. Thus, oxidation of the enaminones **291** and **292** gives the isoxazoloquinones **293** and the naphth[2,3-*c*]isoxazoloquinone **294,** respectively, Scheme 80 (74S30; 85JHC697).

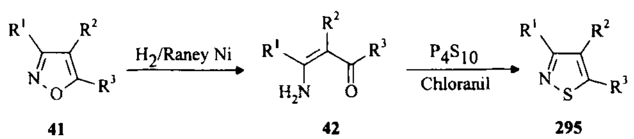


SCHEME 80

Other reported methods for isoxazole synthesis are the 1,3-cycloaddition of nitrile oxides to 1,3-cyclohexadione-derived enaminones (78S43), the thermolysis of 2,2-diacyl-*N*-(1-pyridinio)vinylamidines [73JCS(P1)2580] and the Knoevenagel condensation of enaminones with isoxazolinone acetate (85JHC127).

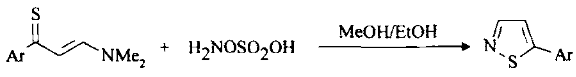
H. ISOTHIAZOLES

Isothiazoles are readily prepared from isoxazoles. Thus, reductive ring opening of isoxazoles **41** gives enaminones **42,** which on treatment with phosphorus pentasulfide and chloranil give the corresponding isothiazoles **295,** Scheme 81. Because isoxazoles are readily available, this method provides a valuable route to a variety of substituted isothiazoles (69T389).



SCHEME 81

Alternatively, treatment of thioenaminones **296** with hydroxylamine-*O*-sulfonic acid gives the isothiazoles **297** in good yields, Scheme 82 (80JOC4857).

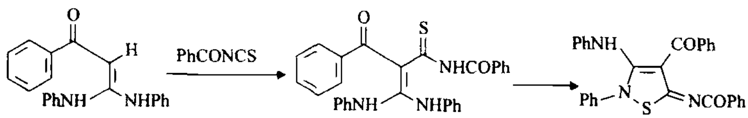


296 297

Ar = aryl

SCHEME 82

A reaction between the enaminone **298** and benzoyl isothiocyanate gave unexpectedly the isothiazole **300**, probably via oxidative cyclization of the acyclic intermediate **299**, Scheme 83 (82S65). Other enaminone analogues gave thioxopyrimidines (Section VI,M,1).



298 299 300

SCHEME 83

I. PYRAZOLES AND PYRAZOLINONES

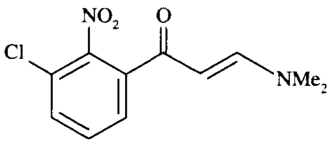
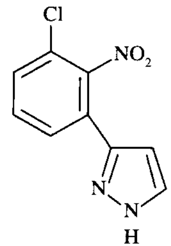
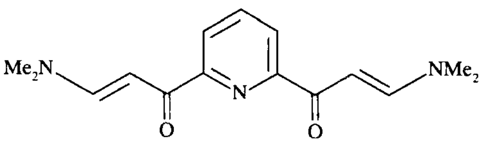
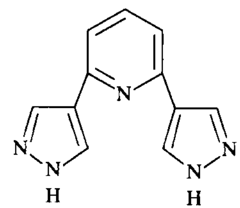
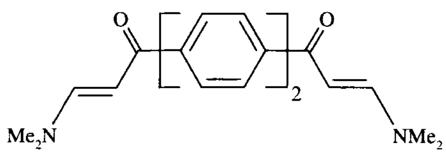
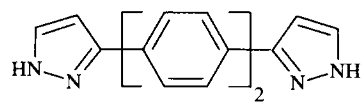
In a synthetic procedure parallel to the preparation of isoxazoles from enaminones and hydroxylamine, the reaction of enaminones with hydrazines present a general approach to pyrazoles. The reaction is usually carried out in alcoholic solution under mild conditions and the pyrazole products often precipitate for easy isolation. Numerous examples are available in the literature; Table III shows some of them.

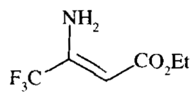
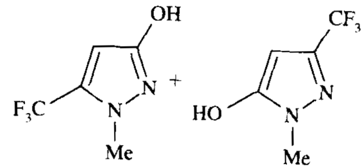
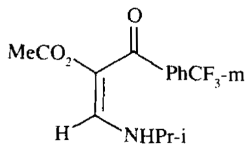
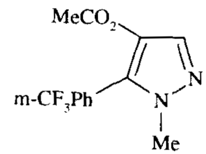
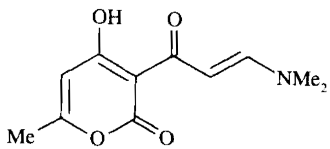
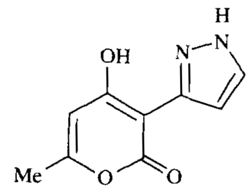
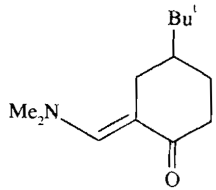
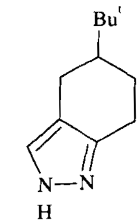
The merit of the method lies not only in the mild conditions required, but also in the easy access to multiply substituted pyrazoles. For example, bi- and tricyclic pyrazoles with powerful dopaminergic activity are synthesized smoothly from the corresponding enaminone (Table III, entry 10) (80JMC481).

A similar reaction between the hydroxyamino enaminones **301** and hydrazine hydrate affords a regiospecific synthesis of 3(5)-alkyl/arylamino-4-nitrosopyrazoles **302** and, under more forcing conditions, 3(5)-alkyl/arylamino-4-aminopyrazoles **303**, Scheme 84 (93JHC129). However, the reactions of enaminones **304** with hydrazines led to the methylthiopyrazoles **305**, because the amino group was unexpectedly the leaving group, Scheme 85 (70ACS3109).

TABLE III

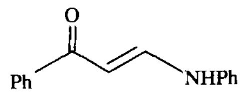
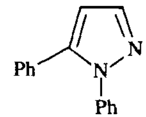
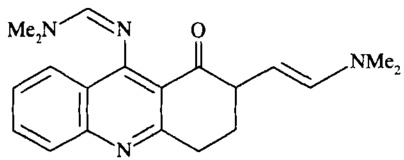
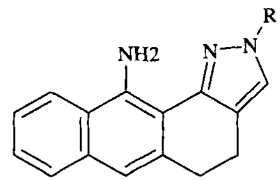
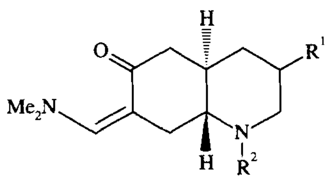
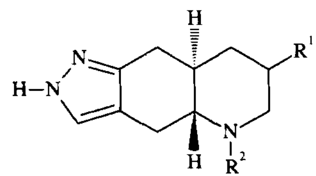
PREPARATION OF PYRAZOLES FROM ENAMINONES AND HYDRAZINES

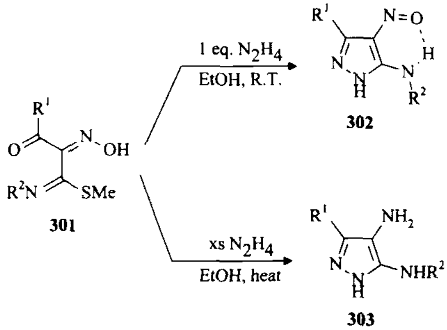
Entry	Enaminone	Hydrazine	Pyrazole	Yield (%)	Ref.
1		NH_2NH_2		88	74JHC275
2		NH_2NH_2		75	77JHC345
3		NH_2NH_2		80	77JHC345

4		$MeNHNH_2$	 85 :15	49	93JHC49
5		$MeNHNH_2$		80	82S318
6		NH_2NH_2		78	77JHC931
7		NH_2NH_2		100	91SC1971

(*continues*)

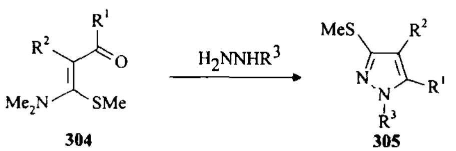
TABLE III (*continued*)

Entry	Enaminone	Hydrazine	Pyrazole	Yield (%)	Ref.
8		$PhNHNH_2$			79T789
9		$RNHNH_2$ R = H, Me		60–67	93JHC23
10		NH_2NH_2			80JMC481



R^1 = aryl; R^2 = alkyl, aryl

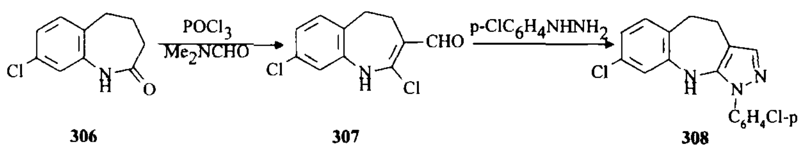
SCHEME 84



R^1 = CN, MeCO, $MeCO_2$; R^2 = Me, 4-BrC_6H_4; R^3 = H, Me, Ph

SCHEME 85

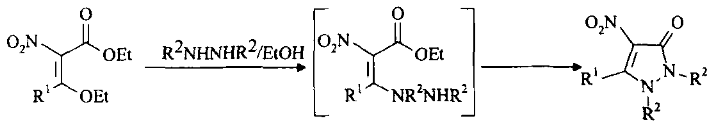
The Vilsmeier–Haack reaction of the benzazepinone **306** gives the enaminone **307,** which, upon treatment with 4-chlorophenyl hydrazine, gives the pyrazole **308.** Pyrazolothiazines and pyrazolo-[4,3-*b*][1,4]-benzothiazines were similarly prepared (72CPB1325).



SCHEME 86

It has been reported that dimedone and 1,3-cyclohexanedione react with hydrazones to give enaminone intermediates, which are converted *in situ* to pyrazoles (73CB450).

By analogy to the preparation of pyrazoles described earlier, the reactions of ethyl β-ethoxy-α-nitroacrylates **309** with hydrazines lead to the enaminone intermediates **310,** which spontaneously cyclize to the 4-nitropyrazolinones **311,** Scheme 87 (77S136).

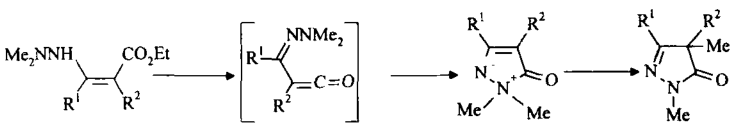


309 310 311

R^1 = H, Me; R^2 = H, Me, Ph

SCHEME 87

Flow pyrolysis of enaminones **312** at 400°C gives the pyrazolinones **315** in moderate yields, Scheme 88. The pyrazolinium ylides **314** can be isolated if the pyrolysis is conducted at a lower temperature (380°C). This suggested a concerted [1,4] elimination of ethanol to give the intermediate ketene **313**, which undergoes electrocyclization to the ylide **314**. A [1,3] methyl shift from nitrogen to carbon finally gives **315** [83JCS(CC)1144].

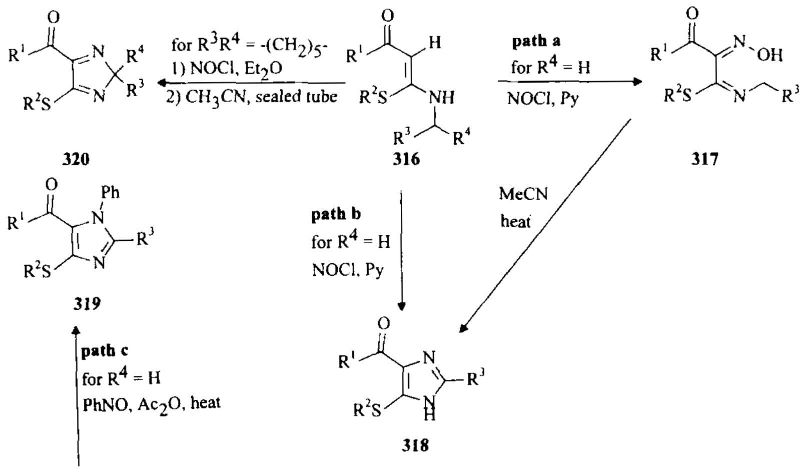


312 313 314 315

SCHEME 88

J. IMIDAZOLES

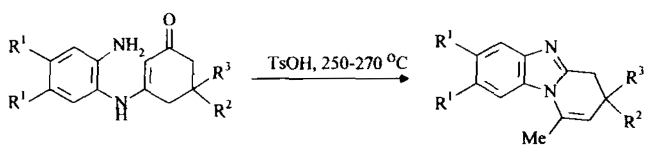
A novel synthesis of imidazoles was reported by Junjappa and co-workers [84JCS(CC)430], in which the reaction of enaminones **316** (R^4 = H) with nitrosyl chloride gives the nitrosoenaminones **317**, which are cyclodehydrated to the 1-*H* imdazoles **318** in high yields, Scheme 89 (path a). The transformation can be done in one step with some of the enaminones under more forcing conditions (path b). Also, 1-phenylimidazoles **319** can be prepared by heating the enaminones **316** (R^4 = H) with nitrosobenzene in sealed tubes (path c). The method was successfully extended to the synthesis of 2,2-disubstituted 2-*H* imidazoles **320** for enaminones **316** ($R^4 \neq$ H) (87S547). Tetrahydrobenzimidazoles are prepared similarly from the cyclodehydration of α-nitroso enaminones derived from 1,3-cyclohexanediones (80JHC1723).



R^1 = Me, Et; R^2 = Me, Et, $PhCH_2$; R^3 = H, Me, Ph, CO_2Et

SCHEME 89

The synthesis of 3,4-dihydropyrido[1,2-*a*]benzimidazoles **322** was achieved by catalytic cyclodehydration of the enaminones **321** at elevated temperatures, Scheme 90 (78S451). The formation of benzimidazoles **322** may involve several rearrangement intermediates.



321 **322**

R^1, R^2 = H, Me; R^3= H, Me, Pr^i, Ph

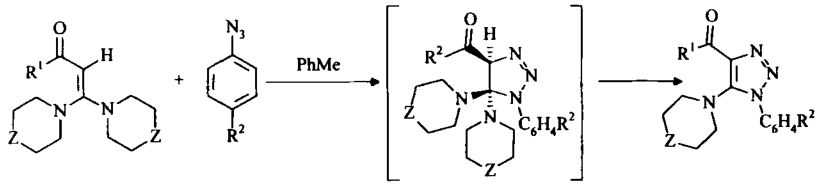
SCHEME 90

Other imidazole syntheses include the photoinduced rearrangement of 1,2,4-oxadiazole-substituted enaminones (88JHC1551) and the condensation of 1,2-phenylenediamine-derived enaminones with triethyl orthoformate (89H281).

K. TRIAZOLES

1,2,3-Triazoles can be prepared by the [3 + 2]-cycloaddition of azidoarenes to enaminones followed by deamination. As outlined in Scheme 91,

the reactions of the enaminones **323** with azidobenzenes **324** give, via the intermediates **325,** the 1-aryl-1,2,3-triazoles **326** in 17–63% yields (86S1010). This reaction represents a general protocol for the preparation of 1,2,3-triazoles, and numerous examples are reported in the literature (62G1040; 66TL6043; 67G304; 68G949).

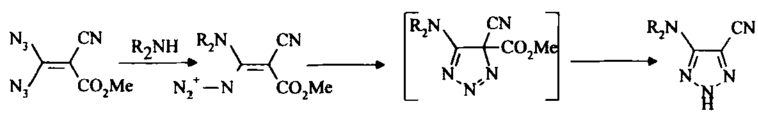


323 **324** **325** **326**

Z = O, N; R^1 = Me, Ph, OMe, OEt, OCH_2Ph; R^2 = Cl, NO_2

SCHEME 91

Similar reactions between methyl 3,3-diazido-2-cyanoacrylate **327** and amines lead to some remarkably stable azido-enaminones **328,** which undergo 1,5-cyclizations to give, probably via the intermediates **329,** the 1,2,3-triazoles **330,** Scheme 92 (87CB2003).



327 **328** **329** **330**

R = Et, R, R = $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NH-(CH_2)_2-$

SCHEME 92

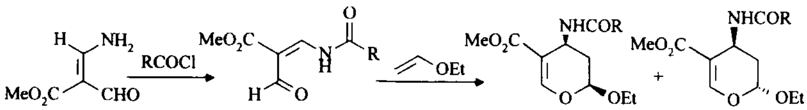
VI. Six-Membered Rings

A. PYRANS AND THEIR DERIVATIVES

1. *Pyrans*

The primary enaminone **331** fails to undergo [4 + 2] cycloaddition with enol ethers, because of its high heterodiene LUMO energy, a consequence of the electron-donating amino group (80AGE779). However, when **331** is acylated, the resulting enaminones **332** are excellent educts and with

ethyl vinyl ether give diastereomeric mixtures of dihydropyrans **333** and **334.** The rate of the cycloaddition is directly related to the electron-withdrawing strength of the acyl group, Scheme 93 (85TL5273).

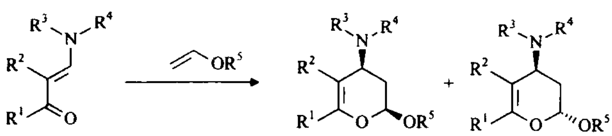


331 **332** **333** **334**

R = Me, Bu^t, CCl_3, Ph, 4-$NO_2C_6H_4$, CO_2Me, PhNH

SCHEME 93

This hetero Diels–Alder reaction allows easy access to a series of pyrans with structures similar to those of the daunosamines. Thus, heating mixtures of *N*-acylenaminones **335** and enol ethers leads to the isomer mixture **336** and **337,** Scheme 94 (86TL6181; 91CB881). In all transformations, the major cis isomers **336** result from kinetic control, which is favored by low temperatures and high pressures. The thermodynamically more stable trans products **337** can be obtained by treatment of **336** with Lewis acids (88JA4065).

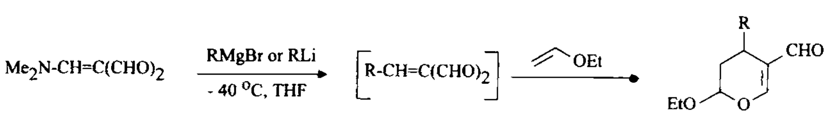


335 **336** **337**

R^1 = CO_2Me, CO_2Et, CCl_3, $CClF_2$, CF_3; R^2 = H, Br; R^3 = PhCO, MeO_2CCO;
R^4 = H; R^3,R^4 = phthaloyl;R^5 = Et, Bu^t

SCHEME 94

Alternatively, Grignard reactions of the enaminone **338** with a variety of reagents are −40°C gave the 1,4-addition intermediates **339,** which were trapped by ethyl vinyl ether to give the dihydropyran derivatives **340,** Scheme 95 (88TL2861).



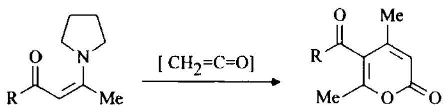
338 **339** **340**

R = alkyl, aryl

SCHEME 95

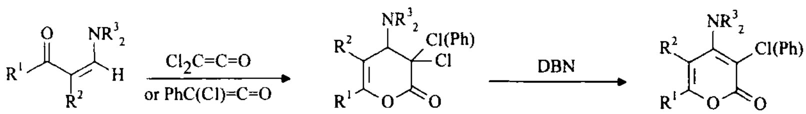
2. *Pyranones*

The 1,4-cycloaddition of ketenes to *N,N*-disubstituted enaminones allows a general synthesis of pyranones. Berchtold and co-workers (61JOC4776; 65JOC2642) showed that treatment of ethyl 3-pyrrolidinocrotonate **341** (R = EtO) or 4-pyrrolidino-3-penten-2-one **341** (R = Me) with an excess of ketene resulted in the formation of pyranones **342**, Scheme 96. The mode of formation of **342** apparently involves initial acetylation with one mole of ketene at the enaminone β position followed by cycloaddition with a second mole of ketene.



SCHEME 96

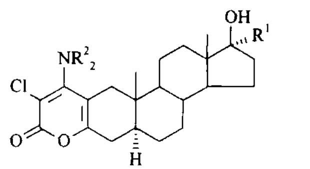
Schenone and co-workers thoroughly investigated the 1,4-cycloaddition of enaminones to dichloroketene [67MC1518; 72JHC1071; 74AC(R)613; 76JHC1201; 77FES794, 77JHC1023; 78JHC181; 79JHC93; 80JHC33; 80JHC507, 80JHC1201; 81JHC111] and phenylchloroketene (85JHC1471; 86JHC1067; 88JHC407). The reactions are generally carried out in anhydrous benzene or toluene at low temperatures (0–5°C) to give 3,4-dihydro-2*H*-pyran-2-ones **344** or 2-pyranones **345** from enaminones **343**, Scheme 97. Enaminones with aromatic *N*-substituents generally give good yields of **344**, which are dehydrochlorinated by a strong base (DBN) to **345**, while those with aliphatic substituents lead directly to **345**, but in low yields.



SCHEME 97

Bi- and tricyclic pyranones such as thio- and benzothiopyrano[4,3-*b*]-pyrans (78JHC181), pharmacologically active furo- and thieno[2,3-*h*]-

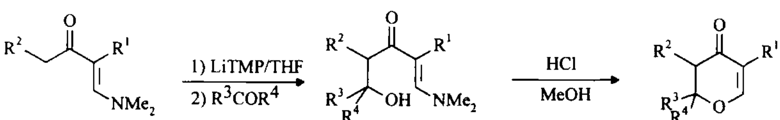
benzopyranones (83MI1; 84FES81; 86FES270; 88JHC407), and the androstane derivatives **346** (89PHA1) are prepared by subjecting the appropriate enaminones to the same reaction sequence.



346

R^1 = H, Me;
R^2 = Me, Et, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$

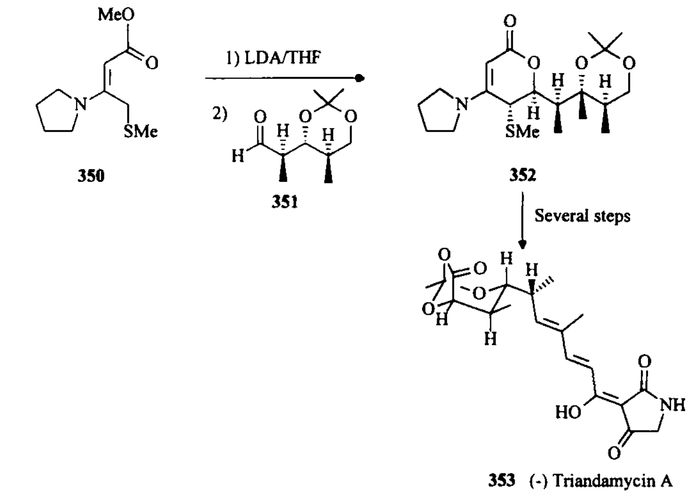
Lithiation of *N,N*-disubstituted enaminones **347** with lithium tetramethylpiperidine (LTMP) in THF generates the α-anions, which are trapped with aldehydes or ketones to give the alcohols **348.** These cyclize with loss of dimethylamine upon acidification to give dihydro-4-pyranones **349** in 37–67% overall yields, Scheme 98 (78TL315).



R^1 = Me, Ph; R^2 = H, Me; R^3 = H, Ph, CO_2Et; R^4 = H, Me, Ph, $PhCH_2$, CO_2Et

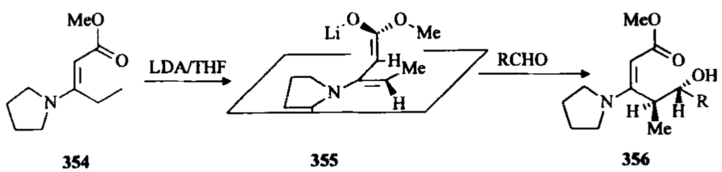
SCHEME 98

Pyrrolidine-derived enaminones without α-protons generally show the best regioselectivity. Treatment of the enaminone **350** with LDA followed by the aldehyde **351** gave the pyranone **352** having a threo configuration of C-4/C-5. This was elaborated on to the antibiotic Tirandamycin A **353,** Scheme 99 (85JA1777). Similar strategies were used in the syntheses of the antibiotic (+)-Rosaramicin Aglycone (86JA3112) and the Prelog–Djerassi lactonic acid (82JA357).



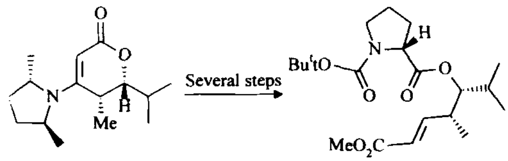
SCHEME 99

The stereoselectivity of the reaction was elucidated for the enaminone **354** by NMR and X-ray studies. Base treatment generates predominantly the enolate **355**, which possesses a twisted diene structure, and the enamine has an E-configuration. Addition of aldehydes to the enolate **355** follows the Cram rule in an antiselective manner to give mainly the adducts **356** having threo configurations, Scheme 100 (86JOC3068; 88JA7901).



SCHEME 100

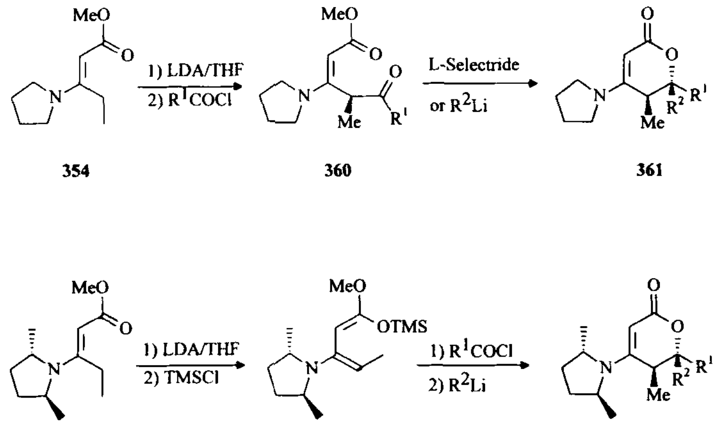
In contrast, lithiation of the enaminone **357**, which contains a chiral dimethylpyrrolidine group, and treatment with isobutyraldehyde follows a syn-selective mechanism to give a single pyranone **358** with the erythro configuration. The pyranone **358** has been converted on to the compound **359**, a fragment of the antibiotic virginiamycin M_2, Scheme 101 (86JOC3070). The difference between **354** and **357** in their selectivity toward aldehydes was a great surprise because spectroscopic and X-ray studies showed that both enolates have remarkably similar solution and solid-state structures (88JA7901)!



358 359

Scheme 101

When the enaminone **354** is treated with an acid chloride in the presence of LDA, a single acylated intermediate **360** is formed. This can be reduced with L-Selectride, or an organolithium reagent can be added to give exclusively a threo pyanone **361** (threo:erythro = 99:1). The enaminone **357** also gives threo pyranones **363**, but only via its trimethylsilyl derivative **362**, Scheme 102 (87JOC708, 87TL5423).



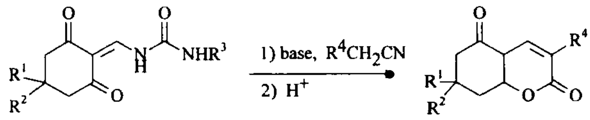
354 360 361

357 362 363

R^1 = Pr^i, Me, Et, Ph; R^2 = H, Me, Et, Bu

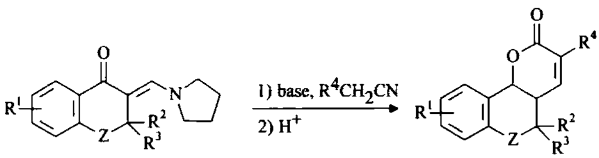
Scheme 102

Pyranones can also be prepared from the Michael addition of active methylene compounds to the appropriate enaminones. Additions of methylene nitriles to the enaminones **364** and **366** under strongly basic conditions followed by acidification give the 2-pyranones **365** and **367**, respectively, Scheme 103 (81S225; 85JHC713). Additions of ethyl acetoacetate to enaminones are also reported to afford 2-pyranones (91CPB1655).



364 365

R^1 = H, Me; R^2 = H, Me, Ph; R^1,R^2 = -$(CH_2)_5$-; R^3 = Me, Et;
R^4 = CO_2Me, CO_2Et, COPh, SO_2Ph, Ph

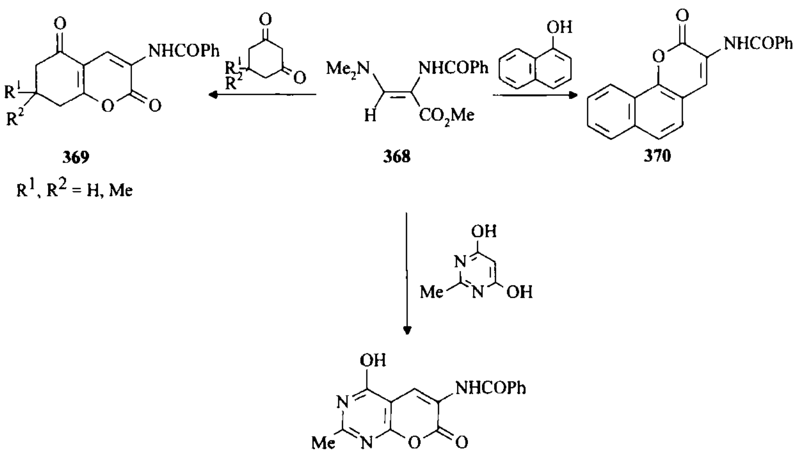


366 367

R^1 = H, 7-OMe, 6-Me; R^2, R^3 = H, Me; R^4 = CO_2Me, CO_2Et, CO_2NH_2;
Z = CH_2, O, NCHO

SCHEME 103

Acid-catalyzed reactions of the enaminone **368** with 1,3-cyclohexanediones, naphthols, or 4,6-dihydroxy-2-methylpyrimidine give the pyranones **369, 370,** and **371,** Scheme 104 (90JHC1021).



369 368 370

R^1, R^2 = H, Me

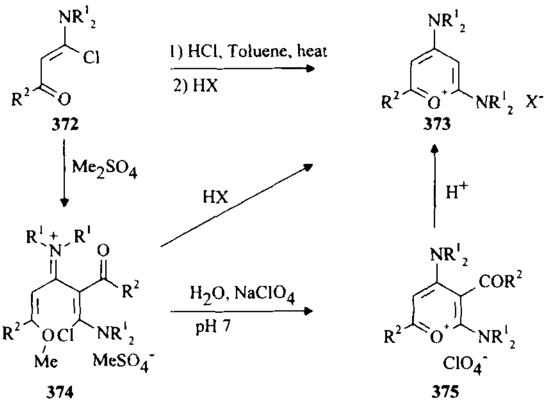
371

SCHEME 104

In addition to the general methods just described, a few others have been mentioned in the literature. Acid-catalyzed cyclization of the enaminones derived from isoxazolylcarbinols (66TL233), double metallation of *N*-amino enaminones followed by quenching with aldehydes (76TL11), and various cyclizations of multifunctional enaminones (77JHC931; 88H2301) are reported to give pyranones.

3. *Pyrylium Salts*

2,4-Bis(dialkylamino)pyrylium salts **373** are readily prepared by treatment of the enaminones **372** with hydrogen chloride in toluene at elevated temperatures. In an alternative approach, cyclization of the methoxy derivative **374** in neutral or acidic conditions gives **375**, which may be deacylated by acid-catalyzed hydrolysis to **373**, Scheme 105 (85TL3963).



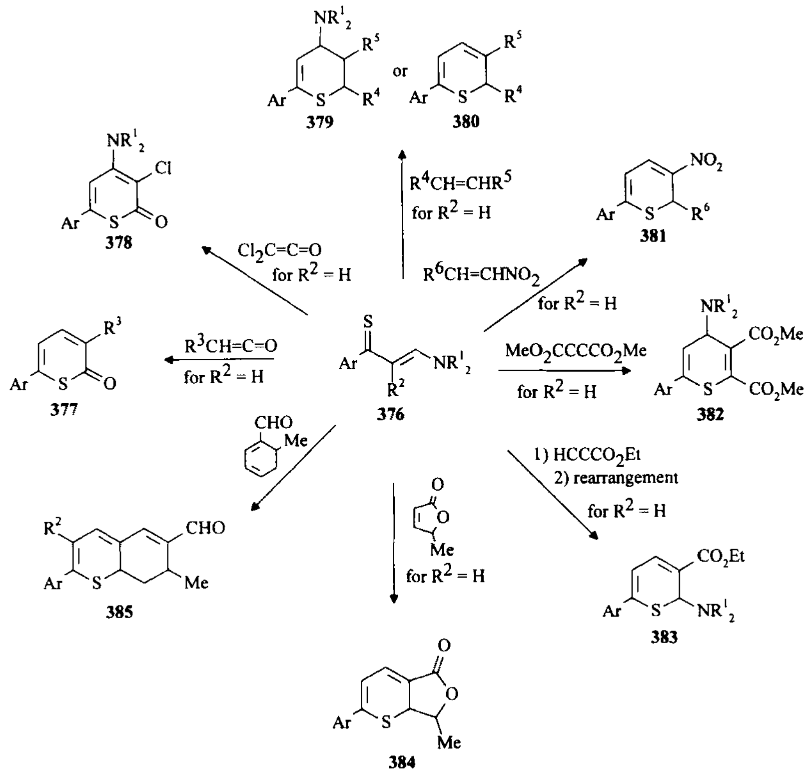
$NR^1{}_2$ = NMe_2, pyrrolidinyl; R^2 = Me, Ph; X^- = ClO_4^-, BF_4^-, Cl^-

SCHEME 105

4. *Thiopyrans*

The [4 + 2] cycloadditions of thioenaminones with dienophiles have been widely exploited in recent years by Quiniou [71CR(C)148; 72BSF2571; 73AC(R)563; 75CR(C)677, 75T2679, 75T3059; 76BSF991; 78CR(C)553], Lawesson (81T3693; 82T1705), and several others [70CPB2469; 87S456; 89ZC57; 90T1951; 92JCS(P1)2603] as a fruitful avenue to functionalized 2*H*- and 4*H*-thiopyrans. A review summarizing the work prior to 1981 was

published (81PS1). In general, enaminones are converted to thioenaminones in good yields by Lawesson's reagent (81T197; 85T5061), and cycloadditions are carried out in benzene. Scheme 106 summarizes typical reactions of this type.

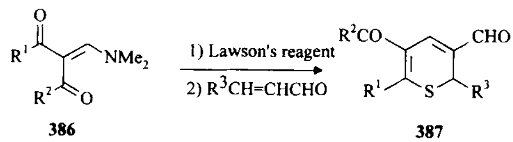


NR^1_2 = NMe_2, pyrrolidinyl, piperidinyl; Ar = aryl; R^2 = H, Ph, p-$MeOC_6H_4$; R^3 = H, Ph; R^4 = H, OEt, SEt; R^5 = CN, COMe, CO_2Me, $CONH_2$, CHO, $CON(COMe)_2$; R^6 = aryl

SCHEME 106

A one-pot thionation/cycloaddition was reported recently [92JCS(P1)-2603]. Treatment of enaminones **386** with Lawesson's reagent generated *in situ* the thioenaminones, which were added to dienophiles to give thiopyrans **387**, Scheme 107. However, no thiopyrans could be isolated

when ethyl cinnamate, acrylonitrile, or phenyl vinyl sulfone was employed as the dienophile.



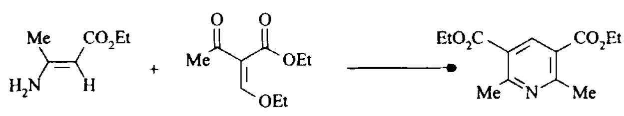
R^1 = Me, R^2 = OEt, R^1R^2 = -$(CH_2)_3$-, C_6H_4O; R^3 = H, Me, Ph

SCHEME 107

B. Pyridines and Their Derivatives

1. *Pyridines*

Claisen reported the first preparation of a pyridine derivative from an enaminone in 1897 with the synthesis of diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate **390** from ethyl 3-aminocrotonate **388** and ethyl ethoxymethyleneacetoacetate **389**, Scheme 108 (1897LA1). Since then this method has been applied to the preparation of many multisubstituted pyridines; a few examples are presented in Table IV. α,β-Unsaturated carbonyl compounds are also excellent substrates for this type of reaction; some examples are shown in Table IV (entries 5, 6, and 8).

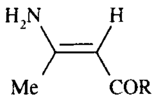
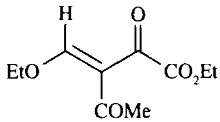
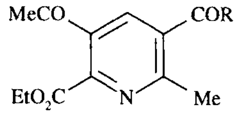
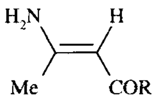
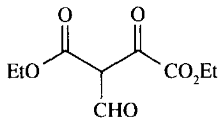
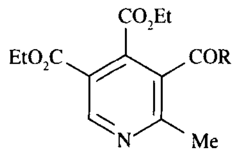
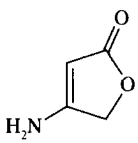
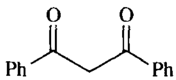
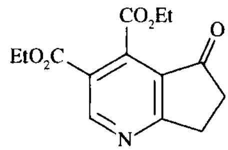
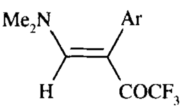
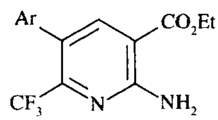
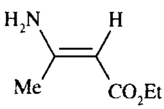
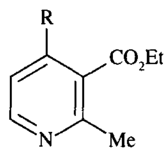
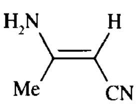
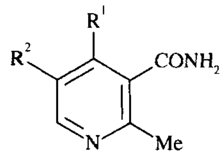
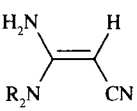
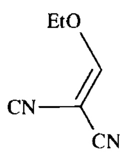
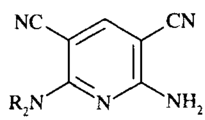
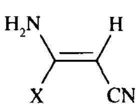
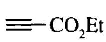
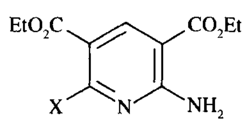


SCHEME 108

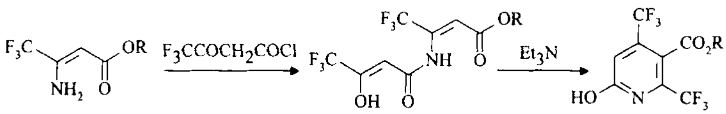
A facile one-pot synthesis of trifluoromethyl-substituted pyridine derivatives has been reported (93JHC71). The procedure depends on the high reactivity of trifluroacetoacetyl chloride, which is generated *in situ* from trifluoroacetyl chloride and ketene. Thus, the enaminone **391** gives the intermediate enamide **392**, which is refluxed in triethylamine to give the

TABLE IV

PREPARATION OF PYRIDINES FROM ENAMINONES AND 1,3-DICARBONYL COMPOUNDS OR α,β-UNSATURATED CARBONYL COMPOUNDS

Entry	Enaminone	Carbonyl compounds	Pyridine	Reference
1				51JA4380
2				51JA5244
3				70CB2403
4	 2 : 1	EtO2CCH2C(═NH)OEt		93JHC37
5		RCH═CHCHO		56JOC800
6		RICH═CHCOR2		93JHC277
7				93JHC253 89JHC1859 90JHC1143
8	 2 : 1			81S227

pyridine **393** in an overall yield of about 58%, Scheme 109. Chlorodifluoro pyridine derivatives can be prepared similarly. The previous methods using hexafluoroacetylacetone as the starting material usually give low yields (65JOC3377; 76JMC43; 83JMC1650).



391 **392** **393**

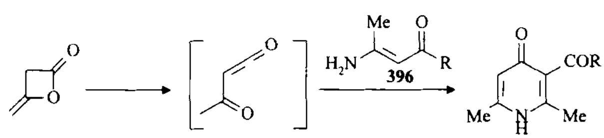
R = Me, Et

SCHEME 109

The reactions between isoxazoles and 1,3-dicarbonyl compounds to give pyridines in multistep syntheses were reported to involve enaminone intermediates (71JOC2784).

2. *Pyridones*

Diketene **394** reacts with the enaminones **396** to provide a general preparation of 4-pyridones **397**, Scheme 110 (69M132; 72S42; 83CPB4300).

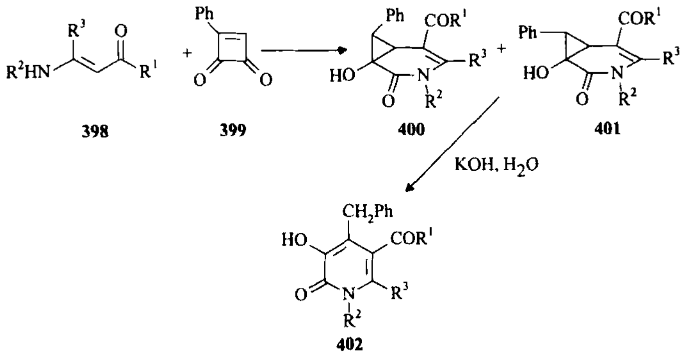


394 **395** **397**

R = Me, Ph, OEt

SCHEME 110

Enaminones **398** and phenylcyclobutenedione **399** react to give mixtures of the 1 : 1 adducts **400** and **401**, which are treated with base to give the 3-hydroxy-2-pyridones **402**, Scheme 111 (69LA230; 71AGE735; 72LA1).

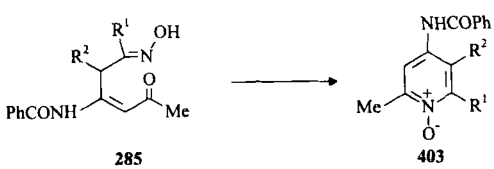


R^1 = Me, Ph, OMe, OEt, NH_2; R^2, R^3 = H, Me, Ph, $PhCH_2$

SCHEME 111

3. *Pyridine N-Oxides*

Pyridine *N*-oxides **403** are synthesized via the sterically hindered enaminone **285** [R, R^1 = $-(CH_2)_3-$ or $-(CH_2)_4-$, see Scheme 78 (89H1443).

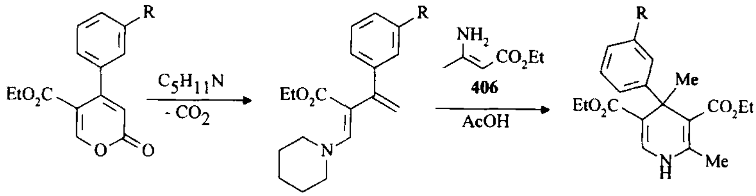


R^1R^2 = $-(CH_2)_3-$, $-(CH_2)_4-$

4. *Dihydropyridines*

Dihydropyridines, which in many cases are generated as pyridine precursors, can be synthesized by condensation of 1,3-dicarbonyl compounds and/or α,β-unsaturated carbonyl compounds with enaminones. These reactions can be considered as variations of the Hantzsch reaction (1882LA1), which goes via an enaminone intermediate and an α,β-unsaturated carbonyl compound (87T5171). Reviews (72CRV1; 82CRV223; 84CHC) on the syntheses of dihydropyridines, especially 1,4-dihydropyridines, have described many of these reactions. Recent studies have focused on the synthesis of 4-substituted or 4,4-disubstituted 1,4-dihydropyridines because of their physiological activity as calcium channel blockers. Thus, treatment of the α-

pyrones **404** with piperidine gives, via cleavage of CO_2, the enaminones **405,** which condense with the enaminone **406** to form the 4,4-disubstituted dihydropyridines **407,** Scheme 112 (87ACE790).

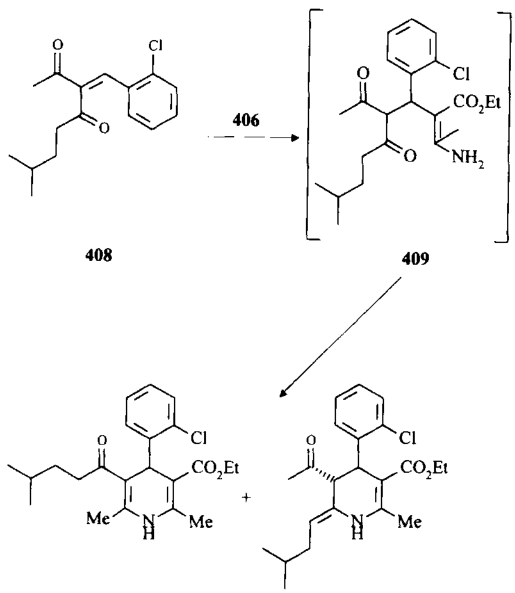


404 **405** **407**

R = NO_2, COMe, COEt

SCHEME 112

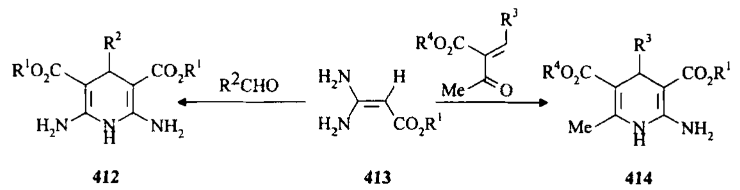
An interesting example of the Hantzsch reaction is depicted in Scheme 113, in which a mixture of the expected product **410** and the exomethylene tetrahydropyridine **411** was obtained from the dione **408** via intermediate **409** (88JHC125). The formation of **411** was assumed to arise from condensation of the enaminone nitrogen with the isopentyl ketone, but the direction of dehydration was unusual and led to the exocyclic double bond.



408 **409** **410** **411**

SCHEME 113

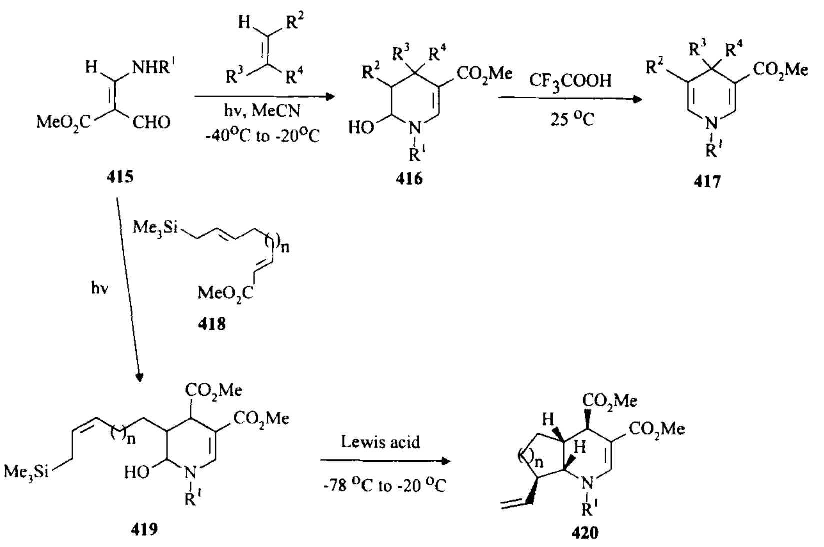
Meyer and co-workers (76LA1762; 77LA1888, 77LA1895; 78LA1476) reported a series of preparations of 2-aminodihydropyridines, which are not readily prepared by the Hantzsch reaction. Typically, an aldehyde is condensed with two equivalents of an enaminone **413** to give a 2,6-diaminodihydropyridine **412.** Alternatively, an α,β-unsaturated ketone condenses with one equivalent of **413** to give a 2-aminodihydropyridine **414,** Scheme 114.



R^1 = Et, Pr^i, Pr; R^2, R^3 = Me, aryl; R^4 = Me, Et, Pr

SCHEME 114

Photocycloadditions of enaminones **415** with alkenes that have either electron-withdrawing or electron-donating substituents give regioselectively the 2-hydroxy-1,2,3,4-tetrahydropyridines **416,** which are dehydrated to give 1,4-dihydropyridines **417,** Scheme 115 (79AGE540; 82AGE539;



R^1, R^2, R^3, R^4 = H, alkyl, ester

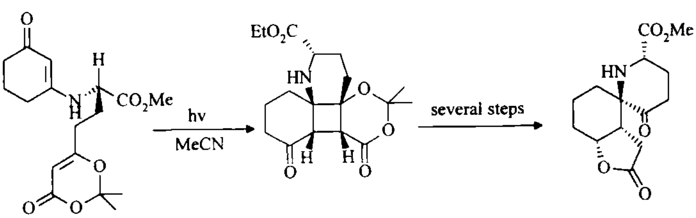
SCHEME 115

83TL3579; 85AGE127; 86S190). The authors suggest that the reaction proceeds via a cyclobutane derivative (the photoaddition product) followed by hetero-retro-aldol cleavage and recyclization to the 2-hydroxytetrahydropyridine [86S190]. The method has a broad scope and provides easy access to heterocycles such as the dihydropyridine nucleosides (85AGE127).

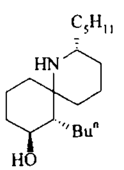
Because the conjugated olefine of **418** is activated by the ester group, photocycloadditions of the alkenes **418** to **415** give predominantly the 2-hydroxytetrahydropyridines **419,** which, after chromatographic separation, are transformed into the tetrahydropyridines **420** by treatment with a Lewis acid (CF_3COOH, $SnCl_4$, etc.), Scheme 115 (91AGE1697).

5. *Piperidines*

When enaminone **421,** prepared in several steps from cyclohexane-1,3-dione and L-methyl glutamate, was irradiated in acetonitrile, a single photoadduct **422** was obtained in a quantitative yield. The exclusive formation of **422** was explained by the pseudo-equatorial position of the ester group, which is more favorable than an axial position in the transition state. Further elaboration of **422** gave the azaspiroundecane **423,** Scheme 116 (86TL5177). This procedure has been used successfully in the synthesis of (−)perhydrohistrionicotoxin **424,** a neurotoxin (89JA4852).



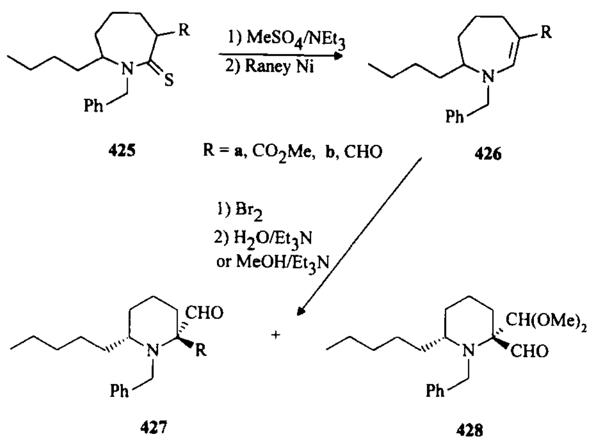
421 **422** **423**



424

SCHEME 116

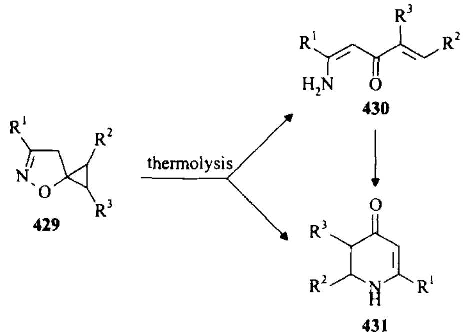
The ring contraction of seven-membered enaminones constitutes an amenable construction of 2,2-bifunctionalized piperidines [82JCR(S)276, 82JOC1688; 86BCJ2353; 89JOC4419]. Methylation/deprotonation of thiolactams **425a,b** followed by desulfurization gives the enaminones **426a,b.** Treatment of **426a** with bromine followed by water/triethylamine gives a single piperidine product **427** (R = CO_2Me). However, **426b** is treated with bromine followed by methanol/triethylamine to give **427** [R = $CH(OMe)_2$] and **428** as a diastereoisomeric mixture, Scheme 117 (89JOC4419). These are alternative starting materials for the synthesis of azaspiroundecanes; compound **427** (R = CO_2Me) was elaborated on to give perhydrohistrionicotoxin **424.**



SCHEME 117

6. *Hydropyridones*

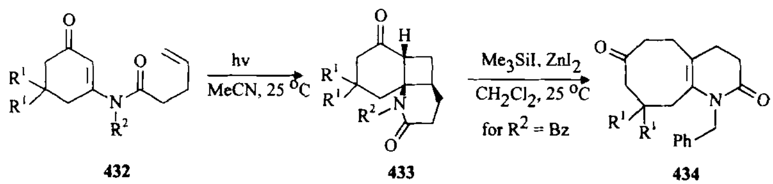
The rearrangement of isoxazoline-5-spirocyclopropanes **429** gives the dihydro-4-pyridones **431.** The rearrangement has been carried out under various conditions, but flash vacuum pyrolysis gives the best yields. The isolation of the enaminone **430** as a sole by-product in many cases strongly suggests that it is the reaction intermediate, Scheme 118 [85JCS(CC)1518; 88JOC2426, 88JOC2430].



R^1 = Me, Ph, Bz; R^2 = H, Ph; R^3 = H; R^2R^3 = $-(CH_2)_4-$

SCHEME 118

Photolysis of enaminones **432** gives tricyclic tetrahydropyridones **433** in good yields. Ring-opening of **433** affords bicyclic dihydropyridones **434**, Scheme 119. Both **433** and **434** are useful synthons for the preparation of triquinanes and various sesquiterpenes (92TL7347).



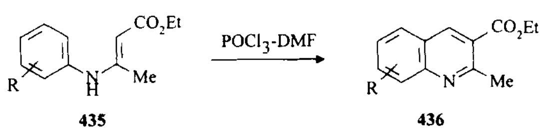
R^1 = H, Me; R^2 = n-C_6H_{13}, Bz, N-piperidino, (S)-1-phenylethyl

SCHEME 119

C. Quinolines and Their Derivatives

1. *Quinolines*

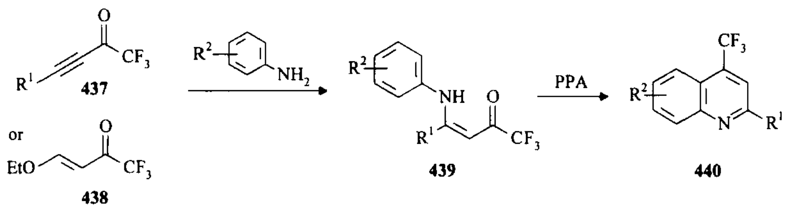
An interesting synthesis has been reported in which a quinoline derivative **436** is obtained from the Vilsmeier reaction of an enaminone **435**. The normal Vilsmeier product spontaneously cyclizes, Scheme 120 (83TL517).



R = NO_2, MeO

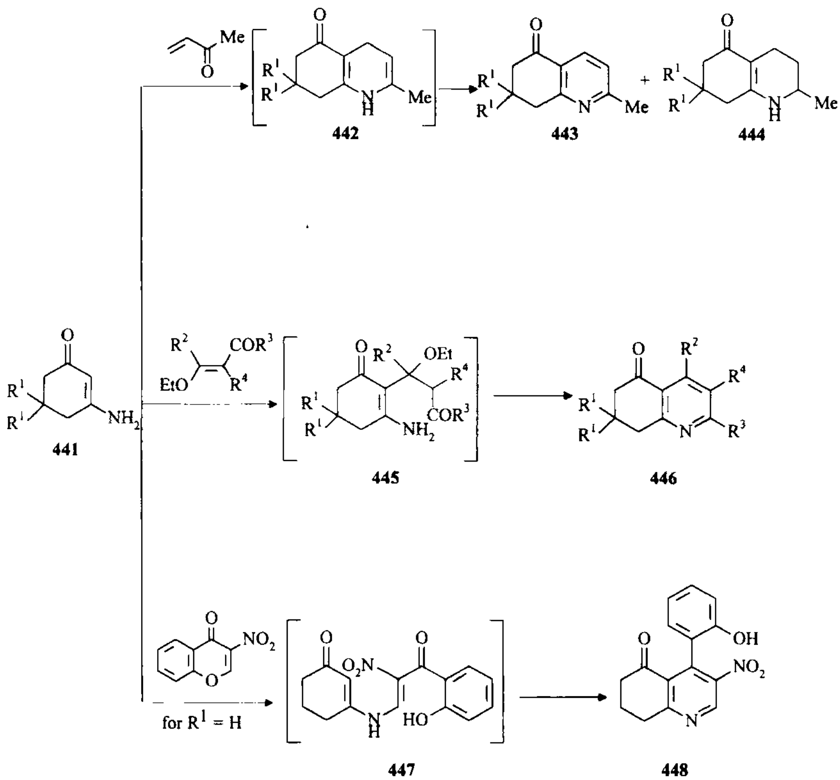
SCHEME 120

The addition of an aniline to an unsaturated trifluoromethyl ketone **437** or **438** provides a facile preparation of an enaminone **439.** In polyphosphoric acid (PPA), this cyclizes to a 4-trifluoromethyl quinoline **440,** Scheme 121 (89TL6173; 90TL2689).



$R^1 = H, n\text{-}C_6H_{13}, n\text{-}C_8H_{17}, Ph; R^2 = OMe, Br, Cl$

SCHEME 121

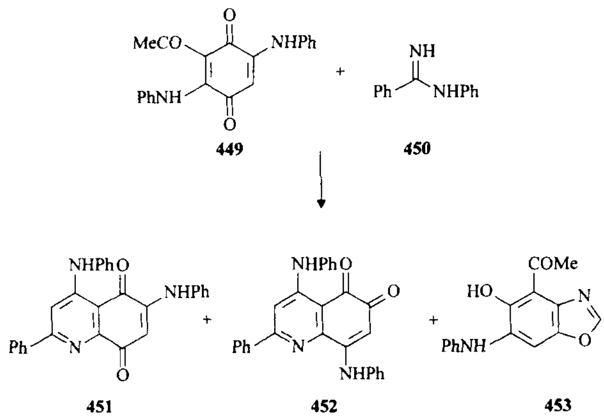


$R^1, R^2, R^3, R^4 = H, Me$

SCHEME 122

The enaminones **441** react with 1-buten-3-one in acidic conditions to give a mixture of the quinolin-5-ones, **443** and **444,** which were assumed to form via disproportionation of the intermediate **442** [79JCS(P1)1411]. The reaction between **441** and an enol ether, however, gives an intermediate **445,** which dehydrates to a quinolin-5-one derivative **446** [70T5907, 70TL3291; 76JCS(P1)975]. Similar products are obtained when acylic enaminones react with cyclohexane-1,3-diones, reactions which may involve enaminone–ketone equilibria [76JCS(P1)975; 81JCR(S)66]. Michael addition of the enaminone **441** (R^1 = H) to 3-nitrochromone opens the pyranone ring to give the intermediate enaminone **447,** which dehydrates to the quinolinone **448,** Scheme 122 (81JHC619).

Reaction between the enaminone **449** and the amidine **450** gives the quinoline-5,8-dione **451** and trace amounts of the quinoline-5,6-dione **452** and the benzoxazole **453,** Scheme 123. A mechanistic explanation was provided by the authors (77LA1445).

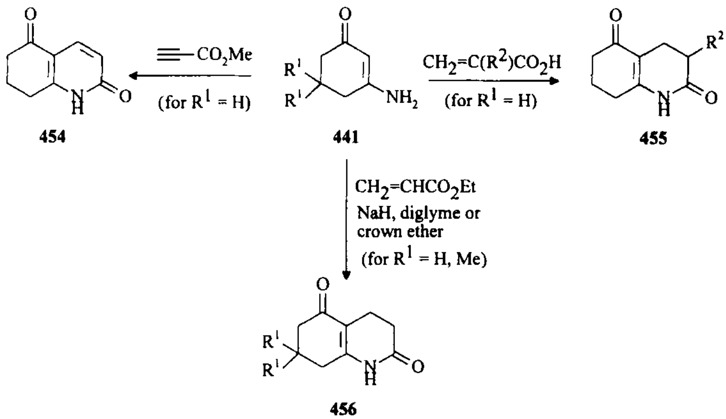


SCHEME 123

2. *2-Quinolones*

2-Quinolones can be prepared in general by Michael additions of cyclic enaminones to α,β-unsaturated esters or acids followed by ring closure. Addition of the enaminone **441** to methyl propiolate gives the 2-quinolone **454** (66TL87; 68JOC1089). Similarly, dihydro-2-quinolones **455** are obtained when acrylic acids or their esters are used (81JOC3719). The reaction of **441** with ethyl acrylate in the presence of base gives either an *N*-alkyl (in THF) or a *C*-alkyl derivative. *C*-Alkylation is followed by spontaneous ring closure to give quinolones **456.** *C*-Alkylation was assumed to result from ion-pairing between the deprotonated nitrogen and the sodium cation

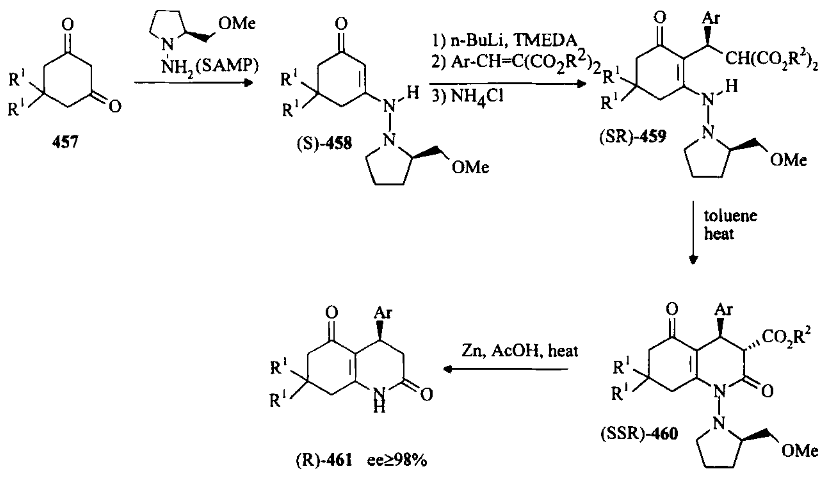
associated with the polyether. As a result, the incoming alkyl group is deflected to C-2 [84JCS(P1)287].



R^1 = H, Me

SCHEME 124

Enders and co-workers developed a highly enantioselective synthesis of 4-aryl-dihydro-2-quinolones by combining enaminone chemistry and asymmetric Michael additions with the SAMP/RAMP-hydrazone method. As shown in Scheme 125, the cyclic 1,3-diketones **457** are transformed into



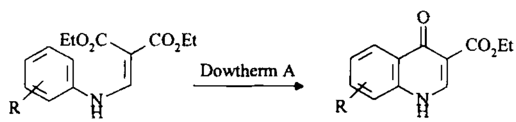
R^1 = H, Me; R^2 = Me, Et; Ar = aryl

SCHEME 125

the chiral enaminones **458,** which are metalated and treated with α,β-unsaturated esters to give the intermediates **459.** Ring closure of **459** gives the quinolones **460,** which are deprotected and decarboxylated to the 4-arylquinolones **461** with high enantiomeric purity and in 50–60% overall yields (87TL3795).

3. *4-Quinolones*

The Gould–Jacobs reaction is a general method for the synthesis of 4-quinolones (4-hydroxyquinolines) (39JA2890). It employs the anilinomethylene malonates **462,** which cyclize under forcing conditions, usually in diphenyl ether or Dowtherm A at high temperature, to give the 4-quinolones **463,** Scheme 126. The general scope and application of the reaction have been reviewed several times (48CRV53; 52HC38), and new syntheses continue to appear. Some recent products of medicinal interest are shown in Table V (entries 1–3).



462 **463**

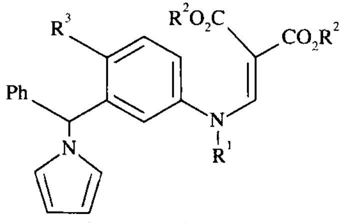
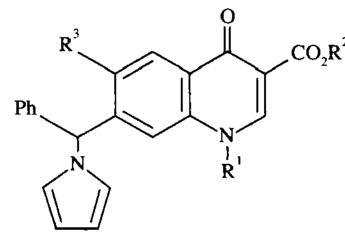
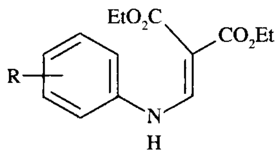
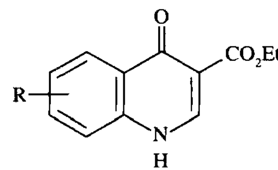
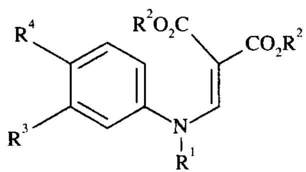
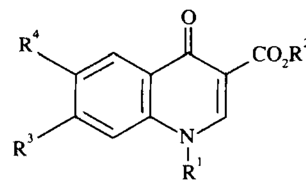
SCHEME 126

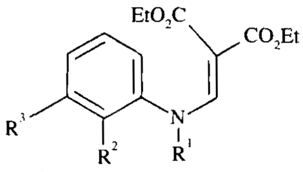
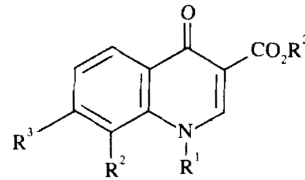
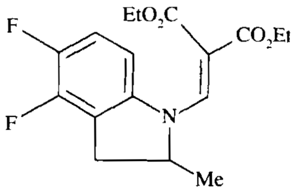
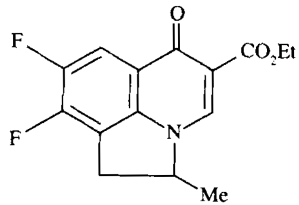
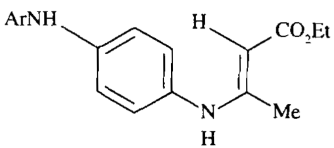
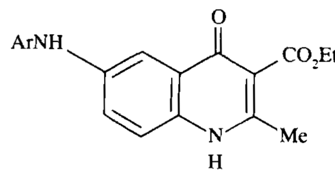
Modifications of the Gould–Jacobs reaction have led to many versatile quinolone syntheses. In Table V, entry 4, ring closure of the tertiary enaminone fails in a high-boiling solvent, but gives the quinolone carboxylic acid with a catalytic amount of phosphorus pentoxide or polyphosphoric acid in refluxing nitrobenzene. This modification is now generally applied to the preparation of quinolones from tertiary enaminones such as the fused quinolone, entry 5 (an important intermediate for fluoroquinolone antibacterials).

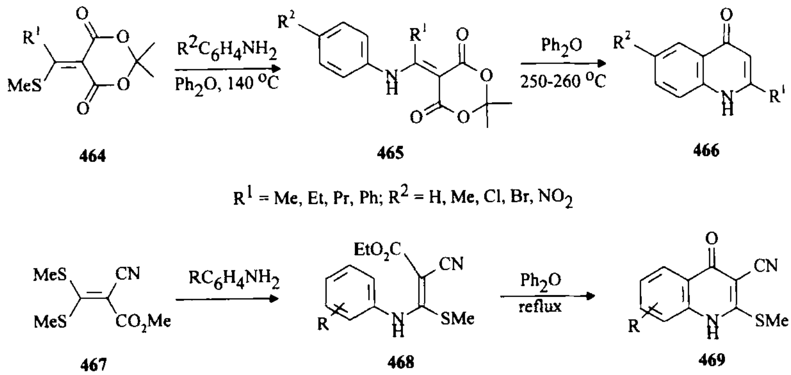
The Conrad–Limpach reaction, which employs β-anilinocrotonates, is also a valued method for 4-quinolone synthesis (1887CB944; 48CRV53; 52HC38), and a recent example is included in Table V (entry 6).

One-pot reactions between the Meldrum's acid derivatives **464** and anilines give the enaminones **465** and, with increased temperature, 4-quinolones **466** in 60–90% overall yields, Scheme 127 (87S482). A similar strategy is used for the preparation of polyfunctionalized quinolones **469,** for which the ketene dithioacetal **467** reacts with anilines to give enaminones **468** followed by ring closure (90JHC1217).

TABLE V
PREPARATION OF 4-QUINOLONES

Entry	Enaminone	Reagents	4-Quinolones	References
1	 R^1, R^2 = H, Et; R^3 = MeO, Cl, F	Dowtherm A		87JHC399
2	 R = o-, m-, p- benzimidazol-2-yl	Dowtherm A		90JHC1177
3	 R^1, R^2 = H, Et; R^3 = H, Me, MeO; R^4 = HO, H_2N, MeO, EtO	Dowtherm A		82JHC289

4	 R^1 = Me, Et, Bu; R^2 = H, Me; R^2, R^3 = benzo	P_2O_5 or PPA		72HCA1319 71JHC357
5		PPA		88JHC1567
6		Dowtherm A		92JMC252



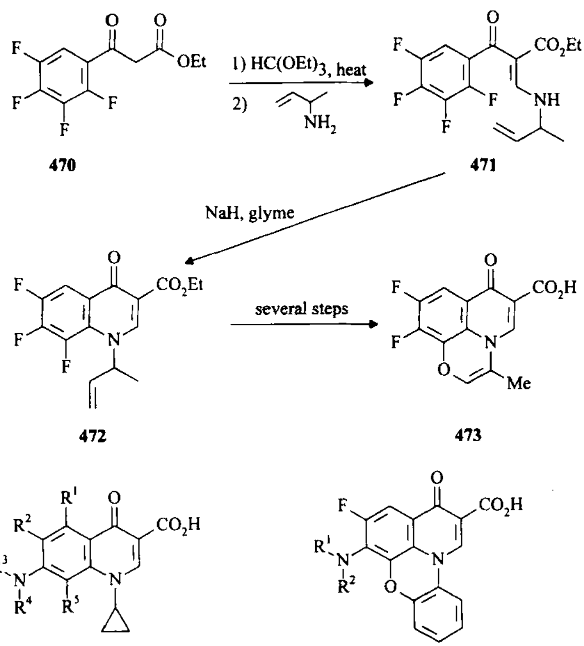
464 465 466

R^1 = Me, Et, Pr, Ph; R^2 = H, Me, Cl, Br, NO_2

467 468 469

R = Me, MeO, Cl, Br

SCHEME 127



470 471 472 473 474 475

R^1,R^2, R^5 = H, F;
R^3,R^4 = $(CH_2)_5$, $CH_2CH(NH_2)(CH_2)_2$

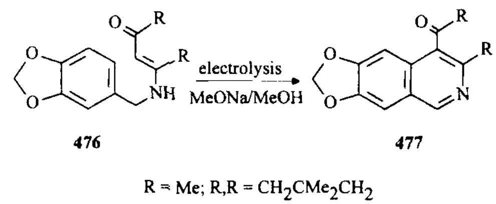
R^1,R^2 = $(CH_2)_2NH(CH_2)_2$,
$(CH_2)_2NMe(CH_2)_2$, $CH_2CH(NH_2)(CH_2)_2$

SCHEME 128

The discovery of the fluoroquinoline antibacterial agents has stimulated considerable interest in the synthesis of fluorinated 4-quinolone-3-carboxylic acids (90MI1, 90MI2). In addition to the methods described previously, an approach where the ring closure is accomplished by the nucleophilic displacement of an *o*-fluorine substituent has been developed (90MI2). Treatment of the ester **470** with triethyl orthoformate followed by 3-amino-1-butene affords the enaminone **471.** Exposure of **471** to sodium hydride leads to the quinolone **472,** which is converted on to **473,** Scheme 128 (90JHC1509). Quinolones **474** (92JMC198) and **475** (87JHC453) are prepared similarly.

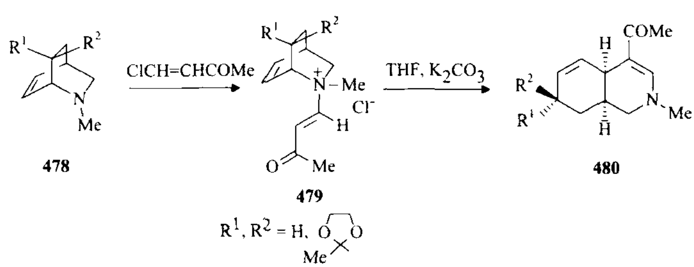
D. Isoquinolines

Anodic electrolysis of enaminone **476** led to an isoquinoline **477** in a fair yield, Scheme 129 (84TL5023).



Scheme 129

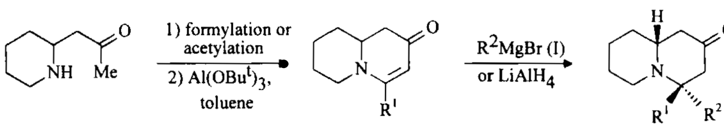
Amine-Claisen rearrangements of the enaminone salts **479,** prepared *in situ* from the tertiary amines **478,** give moderate yields of the hexahydroisoquinolines **480,** Scheme 130 (77TL4299; 79JOC124). The procedure was claimed to offer advantages for the preparation of highly functionalized hydroisoquinolines and was also used in the preparation of hydrophenanthridines (Section VI,G).



Scheme 130

E. Quinolizidines

N-Formylation or acetylation of pelletierine **481** followed by treatment with aluminum *t*-butoxide gives the enaminones **482.** Reduction of **482** (R^1 = CH_3) with lithium aluminum hydride proceeds sterospecifically to give the alkaloid Epimyrtine **483** (R^1 = Me, R^2 = H). Similarly, Michael addition of methyl magnesium iodide to **482** (R^1 = H) gives (±)-Myrtine **483** (R^1 = H, R^2 = Me), Scheme 131 (79TL4587; 81T4287).

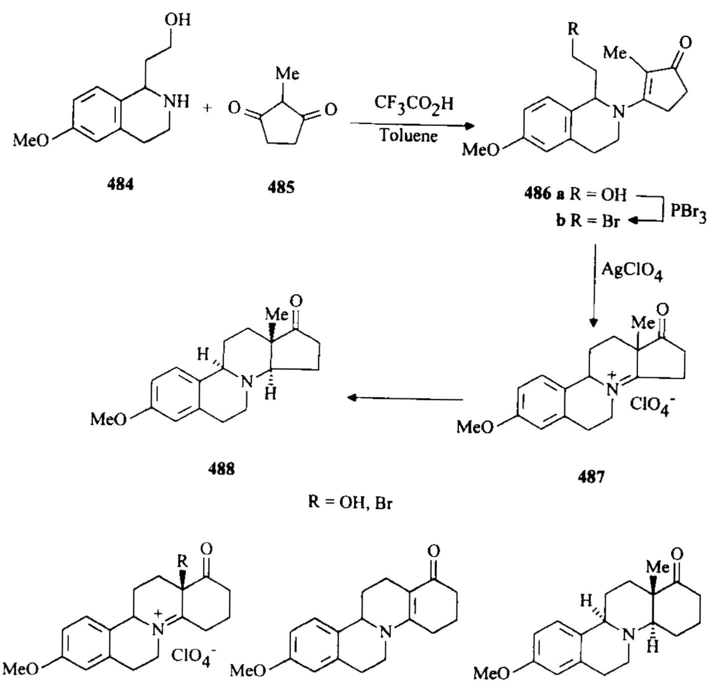


481 **482** **483**

R^1 = H, Me; R^2 = H, Me, Et, Ph

SCHEME 131

Meyers and co-workers showed that condensation of the amine **484** with 2-methyl cyclopentanedione **485** gave the enaminone **486a** (R = OH),



484 **485**

486 a R = OH
b R = Br

488 **487**

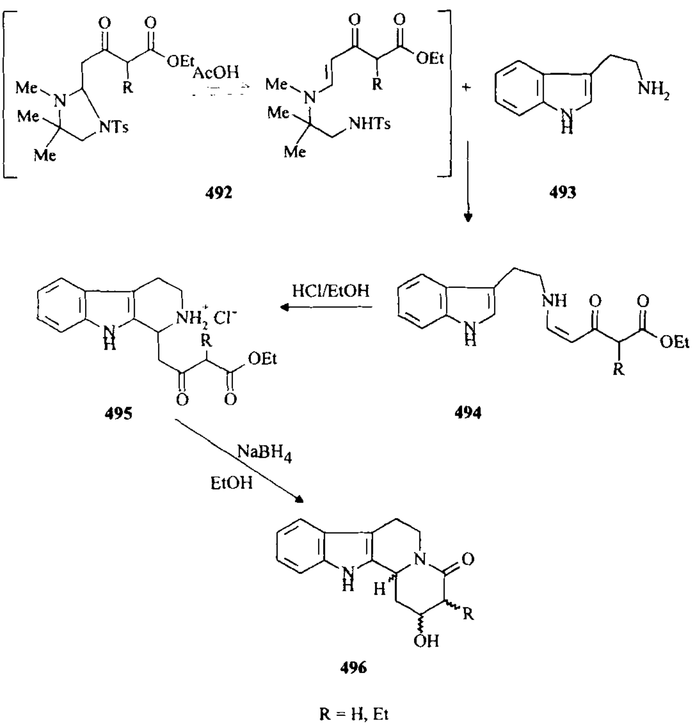
R = OH, Br

489 **490** **491**

SCHEME 132

which was transformed into the bromide **486b** and subsequently cyclized to the intermediate **487**. The salt **487** was unstable, but was hydrogenated to the quinolizidine **488**, Scheme 132. The six-membered analogue **489** (R = H) was similary prepared and smoothly converted to the azasteroid **490** by neutralization, but the homologue **489** (R = Me) gave only a low yield of **491** upon hydrogenation (65JOC3667; 67T785).

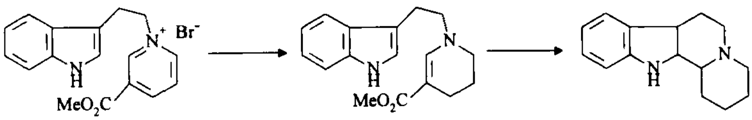
The importance of indoloquinolizidine alkaloids has stimulated the development of synthetic methods. For example, reaction of the compound **492** with tryptamine **493** gives the enaminone **494**. Treatment of **494** with hydrogen chloride gives the β-carboline salt **495**, which is neutralized and reduced to the indoloquinolizidine **496**, Scheme 133 (82TL3301).



SCHEME 133

The naturally occurring indoloquinolizidine **499** was prepared by the reduction of the nicotinic ester salt **497** followed by cyclization, hydrolysis, and decarboxylation of the enaminone **498** (65JA5461). A number of quinolizidines, including yohimboid, ajmalicinoid, and corynantheioid alkaloids,

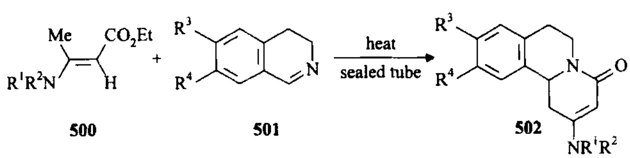
have been synthesized by this procedure (63TL1645; 68ACR78; 76JA3645; 79JA5370; 80JA7971).



497 498 499

SCHEME 134

Condensations of the enaminones **500** with dihydroisoquinolines **501** give the benzoquinolizidines **502** in moderate yields, Scheme 135 (80S996).

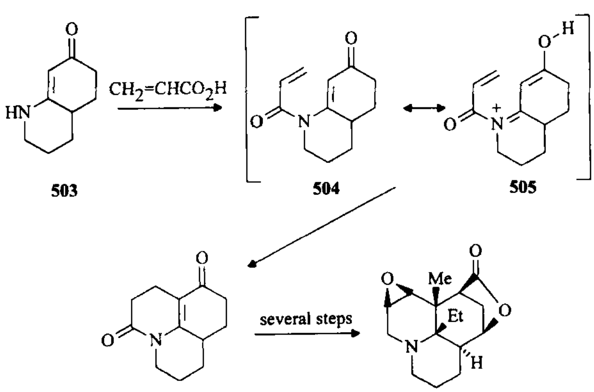


500 501 502

R^1 = alkyl, R^2 = H, Me, Et. R^1R^2 = $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$, R^3, R^4 = H, OMe

SCHEME 135

Attempted construction of the tricyclic enaminone **506** by reaction of **503** with acrylonitrile or methyl acrylate failed, but simple heating of **503** with acrylic acid gave an excellent yield of **506.** The reaction was assumed to go through the intermediates **504** and **505** and was used in the synthesis of the Lycopodium alkaloid annotinine **507,** Scheme 136 (69CJC433).



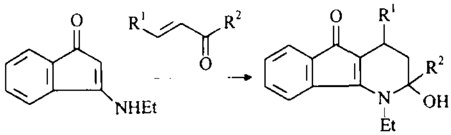
503 504 505

506 507

SCHEME 136

F. Indenopyridines

The enaminones **508** underwent Michael additon to α,β-unsaturated ketones and aldehydes followed by cyclization to give the indenopyridine derivatives **509.** Compound **509,** R^1, R^2 = H, was readily oxidized to the corresponding indenopyridone, Scheme 137 (82AP1043).



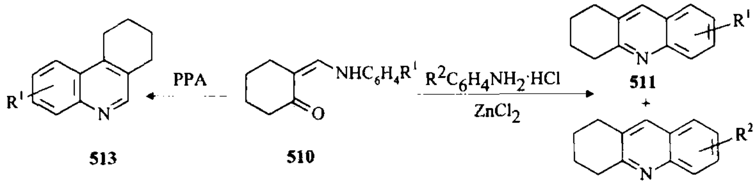
508 **509**

R^1, R^2 = H, Me

SCHEME 137

G. Acridines and Phenanthridines

The preparation of acridines by the acid-catalyzed cyclodehydration of 2-arylaminomethylene-cyclohexanones **510** has been known for many years (10LA70; 42JCS693). When the reaction is carried out with an appropriately substituted aniline hydrochloride and zinc chloride, the expected acridine **511** is obtained. When a different substituted aniline hydrochloride is used, however, a mixture of acridines **511** and **512** is obtained, Scheme 138 [42JCS693; 68JCS(C)2237; 70IJC1]. The preparation of **511** is improved by the use of lactic acid (72IJC9). If polyphosphoric acid is used, a phenanthridine **513** rather than an acridine is obtained [68JCS(C)2237; 70IJC1; 72IJC9]. Bis-anil intermediates were proposed for these reactions (42JCS-693; 70IJC1; 72IJC9; 73TL2821).

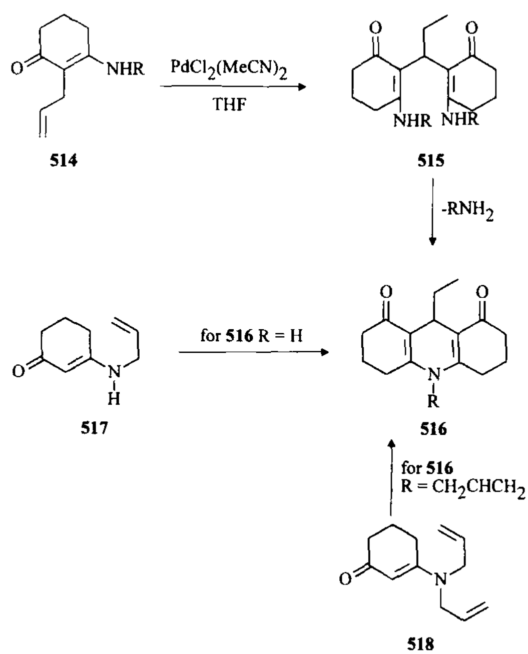


513 **510** **511** **512**

R^1, R^2 = H, Me, OMe, Cl

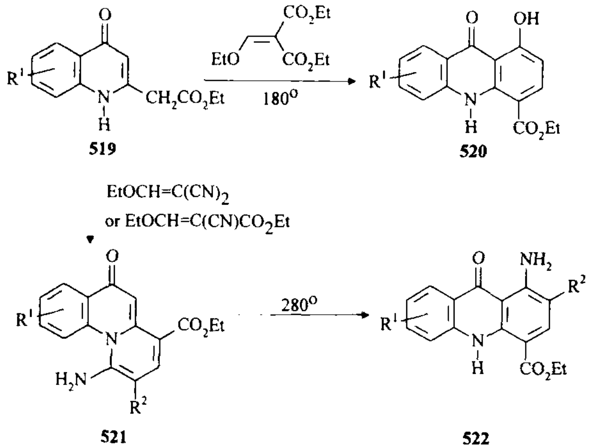
SCHEME 138

The enaminones **514** are refluxed with a catalytic amount of $PdCl_2(MeCN)_2$ in tetrahydrofuran to give acridinediones **516**, presumably via bisenaminone intermediates **515**. The acridinediones **516** are also obtained from the enaminones **517** and **518**. The formation of **516** from **517** and **518** suggests initial sigmatropic rearrangements of **517** to **514** (R = H) and **518** to **514** (R = $CH_2CH{=}CH_2$) [81JCS(CC)114].



SCHEME 139

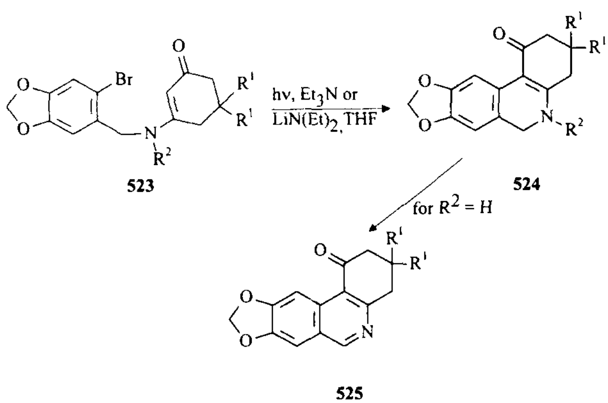
Reactions of the enaminones **519** with diethyl ethoxymethylenemalonate give the acridinones **520** in good yields, with none of the isomers that would result from cyclization onto the nitrogen. When ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate is used, however, the ring closure first occurs at the nitrogen to give the benzoquinolizinones **521**, which isomerize to acridinones **522** at elevated temperatures, Scheme 140 (87JOC3930; 88JHC161).



R^1 = H, MeO; R^2 = CN, CO_2Et

SCHEME 140

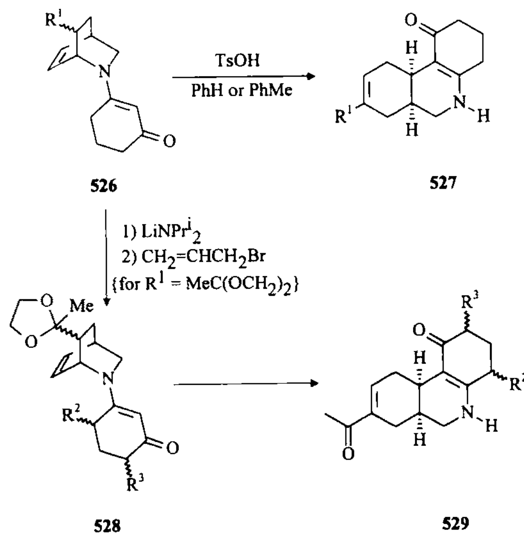
Photolysis of the bromoenaminone **523** (R^1 = Me, R^2 = H) gives the phenanthridone **524** (R^1 = Me, R^2 = H), which is spontaneously oxidized to **525** (R^1 = Me) in a 25% overall yield [78JCS(CC)766]. Treatment of compounds **523** with base also results in formation of the appropriate **524** and, if R^2 = H, of **525**, Scheme 141 (78JA3598; 79JOC1074). Benzyne intermediates were invoked in the latter route. Pyrrolophenanthridine derivatives are also prepared by both methods [75JCS(P1)2502; 78JA3598, 78JCS(CC)766; 79JOC1074; 81CL475].



R^1 = H, Me; R^2 = H, Et

SCHEME 141

Acid-catalyzed amino-Claisen rearrangements of the enaminones **526** provide an entry to the functionalized decahydrophenanthridines **527,** Scheme 142 (77TL4299; 79JOC124; 81JOC4643; 83TL1021). The effect of R^1 on the ease of rearrangement was shown by the length of reaction time as the hydrogen (7 days) changed to the ketal (3.5 days) and to the acetyl (13.5 hours). Lithiation of the enaminone **526** (R^1 = ketal) followed by treatment with allyl bromide gives the derivatives **528** ($R^2 = CH_2CH{=}CH_2$, R^3 = H, or R^2 = H, $R^3 = CH_2CH{=}CH_2$), which undergo deketalization–rearrangement to give the phenanthridine derivatives **529** (81JOC4643). Pyrrolophenanthridine derivatives are prepared similarly (83TL1021).



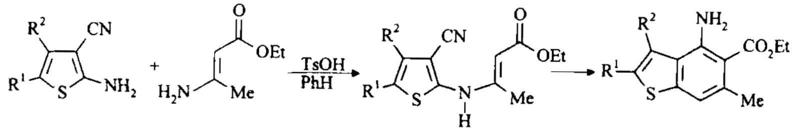
R^1 = H, Ac, $MeC(OCH_2)_2$; R^2/R^3 = H, $CH_2CH{=}CH_2$

SCHEME 142

H. Pyridines Fused to Five-Membered Heterocycles

1. *Thienopyridines*

Reactions of 2-amino-3-cyanothiophenes **530** with the enaminone **531** catalyzed by acid give high yields of the intermediates **532,** which are treated with base to give the thieno[2,3-*b*]pyridine-5-carboxylates **533,** Scheme 143 (79JHC603).

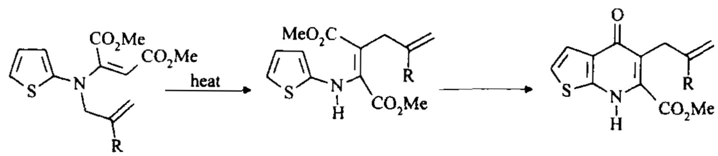


530 531 532 533

$R^1, R^2 = Me, -(CH_2)_3-, -(CH_2)_4-, -(CH_2)_5-$

SCHEME 143

The hetero-Cope rearrangement of the *N*-allyl-*N*-thiophenylenaminone **534** gives the intermediate **535**, which subsequently cyclizes to the thienopyridine **536**, Scheme 144 (73CB368).

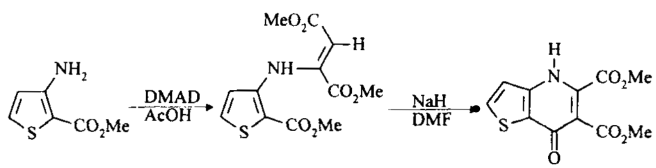


534 535 536

R = H, Cl

SCHEME 144

The Michael addition of 3-amino-2-methoxycarbonylthiophene **537** to dimethyl acetylenedicarboxylate yields the enaminone **538**, which is cyclized in base to give the thieno[3,2-*b*]pyridone **539**, Scheme 145 [78JCR(S)393].

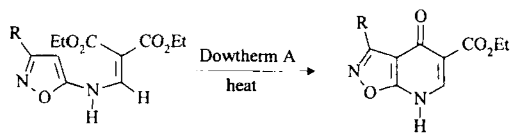


537 538 539

SCHEME 145

2. *Isoxazolopyridines*

The thermal cyclization of enaminones **540** gives the 4-oxoisoxazolo[5,4-*b*]pyridines **541** in good yields, Scheme 146 (88JHC231).



540

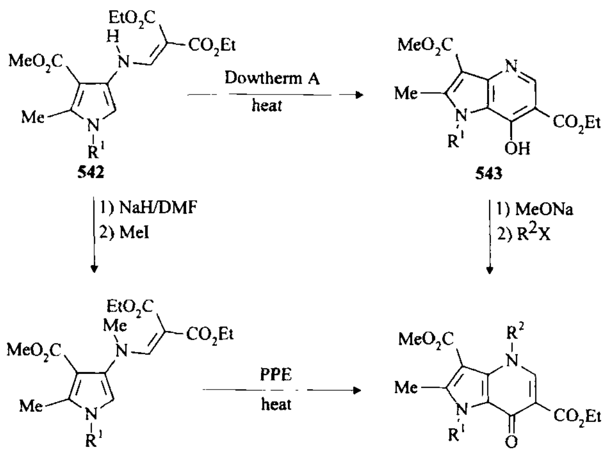
541

R = Me, Ph

SCHEME 146

3. *Pyrrolopyridines*

Thermal cyclization of enaminones **542** gives pyrrolo[3,2-*b*]pyridines **543**, which may be *N*-alkylated to give pyrrolo[3,2-*b*]pyridones **545**. Alternatively, **542** may be *N*-methylated to give the new enaminones **544**, which are cyclized in polyphosphoric ester (PPE) to the pyrrolopyridones **545** (R^2 = Me), Scheme 147 (85JHC83; 90JHC1201).

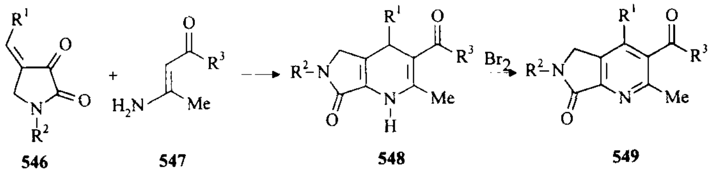


542 543 544 545

R^1 = Me, $PhCH_2$; R^2 = alkyl; X = Br, Cl

SCHEME 147

Condensation of the enaminones **547** with the pyrrolidine-2,3-diones **546** affords the adducts **548**, which on dehydrogenation give the pyrrolo[3,4-*b*]pyridines **549**, Scheme 148 [74JCS(P1)2108].

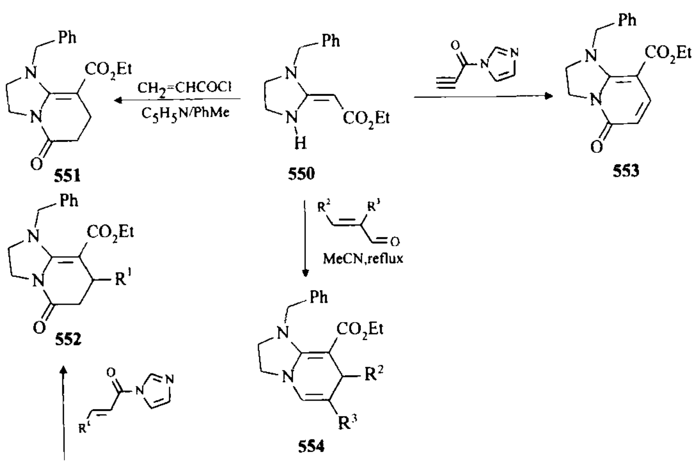


R^1 = aryl; R^2 = alkyl; R^3 = Me, OEt

SCHEME 148

4. *Imidazopyridines*

Enaminones derived from imdazolines are employed as precursors of imidazopyridones and imidazopyridines. For example, the reaction of the enaminone **550** with propenoyl chloride leads to initial *N*-acylation with subsequent conjugate addition to give the hexahydroimidazo[1,2-*a*]pyridone **551** in 82% yield. More conveniently, reactions of **550** with α,β-unsaturated acyl imidazolides give the imidazolopyridones **552** and **553** in excellent yields (88TL5005). The reactions of **550** with enals show initial *C*-alkylation of the enaminone with subsequent cyclization to give the tetrahydroimdazo[1,2-*a*]pyridines **554** (89TL5361).

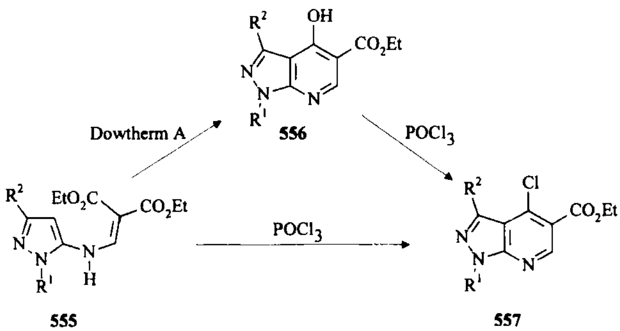


R^1, R^2 = H, Me, Ph; R^3 = H, Me

SCHEME 149

5. *Pyrazolopyridines*

Thermal cyclization of the enaminones **555** gives the 4-hydroxypyrazolo[3,4-*b*]pyridines **556,** which may be converted to 4-chloro analogues **557.** Direct treatment of **555** with phosphorus oxychloride also yields **557,** Scheme 150 (72JHC235).

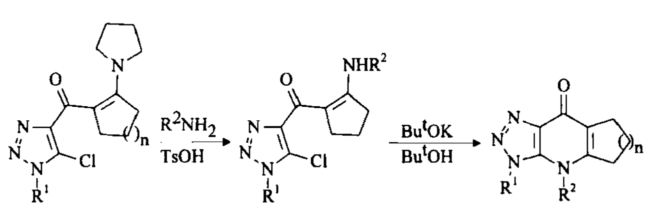


R^1 = alkyl, aryl; R^2 = H, Me, Ph

SCHEME 150

6. *Triazolopyridines*

Transaminations of the enaminones **558** with anilines give the new enaminones **559,** which are treated with potassium *t*-butoxide to give the 1,2,3-triazolopyridine derivatives **560,** Scheme 151 (90JHC1135). The triazolopyridines **560** were elaborated on to other triazolopyridine derivatives.



R^1 = $PhCH_2$, 4-$MeOC_6H_4CH_2$; R^2 = aryl; n = 1, 2

SCHEME 151

I. Pyridines Fused to Six-Membered Heterocycles

1. *Pyridopyrimidines*

Pyrido[2,3-*d*]pyrimidines are usually synthesized by thermal cyclization (the Gould–Jacobs reaction) of enaminones derived from 6-aminopyrimidines and diethyl ethoxymethylenemalonate. The cyclization is generally carried out in Dowtherm or diphenyl ether at elevated temperature and affords overall good yields (Table VI, entry 1).

It appears that an electron-donating group in the pyrimidine moiety is essential for cyclization, but an enaminone with an amino group at the 4 position failed to react. This was overcome by introducing an additional electron-donating methylthio group, and by reducing the inductive effect of the amino group by acetylation (Table VI, entry 2) (72JOC3980).

Thermal and acid-catalyzed cyclizations of the enaminones derived from 2-aminopyridines are general methods for the preparation of pyrido[1,2-*a*]pyrimidines. Early work by Lappin (48JA3348) and others (52JA5491; 58JA3066) showed that, although the pyridopyrimidine is usually the only product, the cyclization can sometimes occur at the C-3 position to give a 1,8-naphthyridine. It has been shown that such naphthyridine formation occurs through the intermediacy of a pyridopymidine which undergoes an acyl migration from N-1 to C-3 [75TL1019; 77JCS(P1)789]. It appears that a mixture of phosphoryl chloride and polyphosphoric acid catalyzes the cyclization more readily and shows selectivity for pyrido[1,2-*a*]pyrimidine formation (Table VI, entry 3). Acetic acid has shown similar selectivity (Table VI, entry 4).

Enaminones react with 1,3-dicarbonyl compounds in the presence of pyridine to give the tetrahydropyrido[1,2-*a*]pyrimidines (Table VI, entry 5).

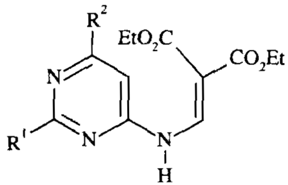
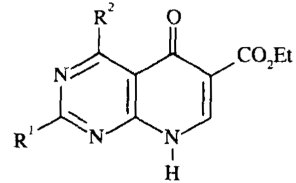
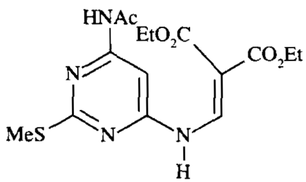
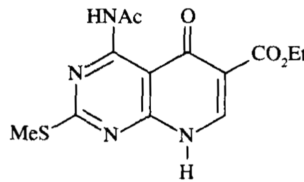
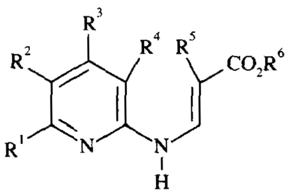
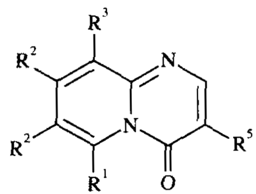
1,3-Dimethyl-6-aminouracil **561** reacts regiospecifically with the enaminone **562** to give the pyrido[2,3-*d*]pyrimidine **563.** The lithium salt of **561** reacts with the imine **564** to give the pyrido[2,3-*d*]pyrimidine **565** (77JOC221).

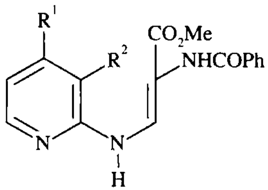
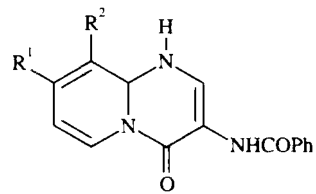
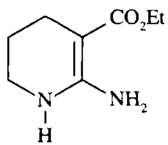
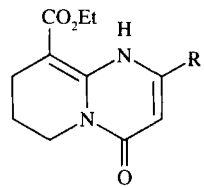
2. *Naphthyridines*

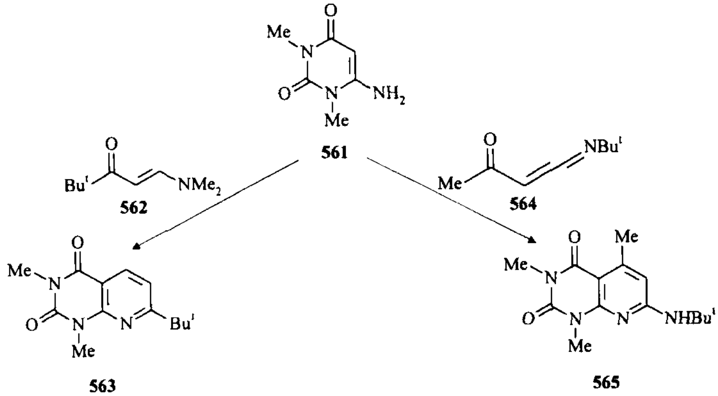
Naphthyridines are generally prepared by thermal cyclization of enaminones derived from aminopyridines. As shown in Table VII, entry 1, thermal cyclization of the enaminone gives the 1,8-naphthridone (from which a series of *N*-alkyl derivatives has been prepared). An isomeric mixture of 1,6-naphthridones can be obtained if both 3 and 5 positions are available (Table VII, entry 2). 1,5-Naphthridines are synthesized from the appropriate enaminones (Table VII, entries 3 and 4).

TABLE VI

PREPARATION OF PYRIDOPYRIMIDINES

Entry	Enaminone	Reagents	Product	References
1	 R^1 = H, Me, OMe, SMe; R^2 = H, Me, OH, Cl	Dowtherm A or Ph_2O		67USP3320257 67JCS(C)1745 70CPB1385 71CPB1482 72JOC3980
2		Dowtherm A		72JOC3980
3	 R^1 = H, Me; R^2, R^3 = H, CO_2Et; R^4 = H, OH; R^5 = alkyl, ester; R^6 = Me, Et	$POCl_3$/PPA		72AF815 77JCS(P1)789 84S152

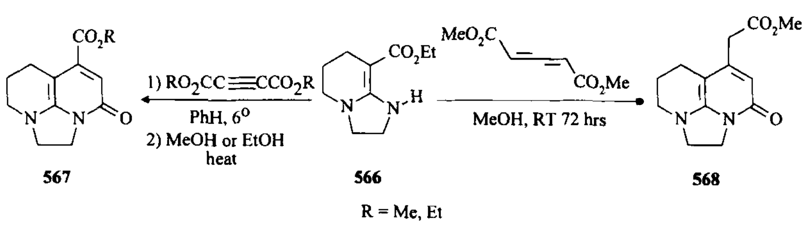
4	 R^1 = H, Me, R^2 = H, NHCH = $C(CO_2Me)NHCOPh$	AcOH		90JHC359
5	 R = Me, Ph	$RCOCH_2CO_2Et$/ C_5H_5N		78CB2813



SCHEME 152

1,4-Dihydropyridines react with *s*-triazine in the presence of sodium hydride to give 1,4-dihydro-1,6-naphthridones in fair to good yields (Table VII, entry 5). Alternative reagents for this reaction are amino-acetals followed by ammonia (Table VII, entry 6). Naphthyridines have also been prepared by the reactions of enaminones derived from cyclohexane-1,3-diones with pentafluorobenzaldehyde in glacial acetic acid (85JHC159).

The cyclic enaminone **566** reacts with acetylenic esters followed by heating in alcohols to give the hexahydroimidazo[1,2,3-*ij*][1,8]naphthyridine derivatives **567** in good yields. When the enaminone **566** is mixed with the allene diester shown at room temperature for 72 hours, the hexahydroimidazonaphthyridine **568** is obtained, Scheme 153 (93S111).



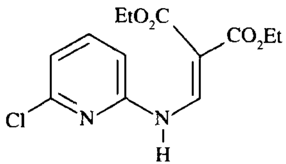
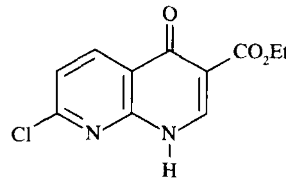
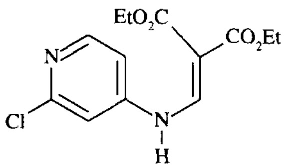
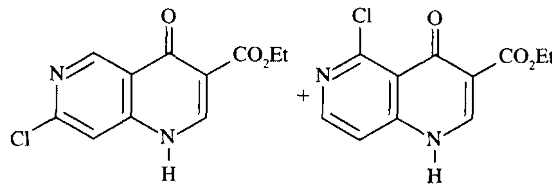
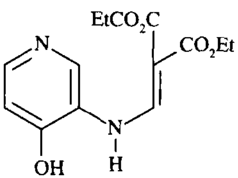
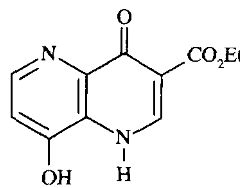
SCHEME 153

3. *Benzopyranopyridines and Benzothiopyranopyridines*

Similar to the fused pyridine syntheses mentioned earlier, benzopyranopyridines and benzothiopyranopyridines are prepared by thermal cy-

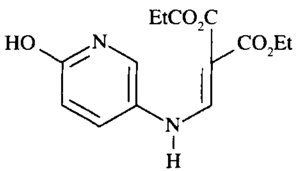
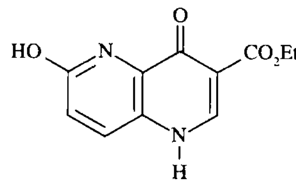
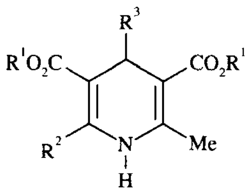
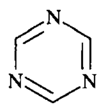
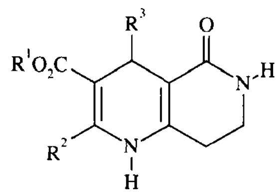
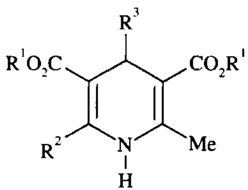
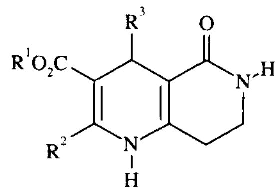
TABLE VII

PREPARATION OF NAPHTHYRIDINES

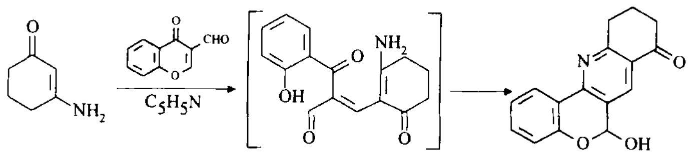
Entry	Enaminone	Reagents	Product	References
1		Ph_2O		82CPB2399
2		Dowtherm A		82CPB2399
3		Dowtherm A		71JOC1331

(*continues*)

TABLE VII (*continued*)

Entry	Enaminone	Reagents	Product	References
4		Dowtherm A		71JOC1331
5		 /NaH		86S859
6	 R^1, R^2 = Me, Et; R^3 = aryl	(1) $(EtO)_2CHNMe_2$ (2) NH_3/EtOH		86S859

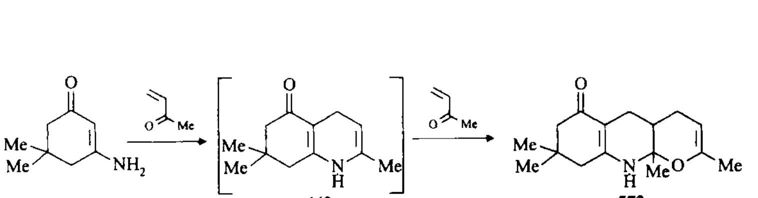
clization of the appropriate enaminoesters (Table VIII, entries 1 and 2). Condensation of acyclic enaminones with 3-formylchromone gives benzopyrano[4,3-*b*]pyridines (Table VIII, entry 3). A possible mechanism for formation of these compounds is shown in Scheme 154 for reaction of the cyclic enaminone **569** to give an intermediate **570,** which could cyclize under the reaction conditions to give the benzopyrano[4,3-*b*]quinoline **571** (78S691; 81JHC607).



569 **570** **571**

SCHEME 154

When the enaminone **441** is treated with methyl vinyl ketone in the absence of acid, it forms the intermediate **442,** which is trapped by excess of the ketone to give the pyranoquinolone **572,** Scheme 155 [79JCS(P1)1411]. More interestingly, the intermediate **442** is also evidently involved in the formation of the benzopyranoquinolone **575** from the trione **573** on refluxing in xylene with ammonia passing. The intermediacy of the methylenedione **574** was explained as resulting from deprotonation of the hydroxy group of **573** leading to elimination of acetone anion, Scheme 156 [79JCS(P1)1411].

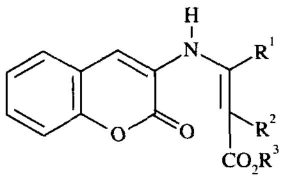
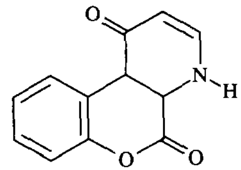
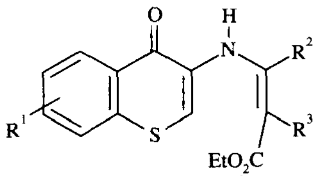
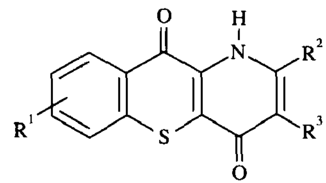
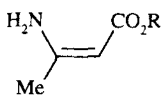
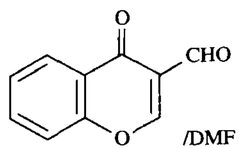
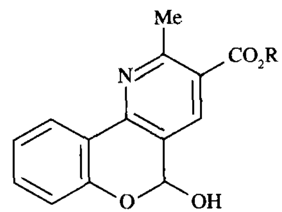


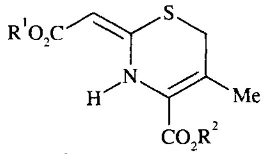
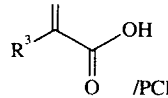
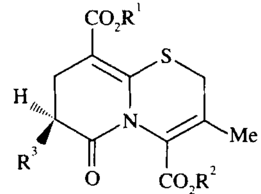
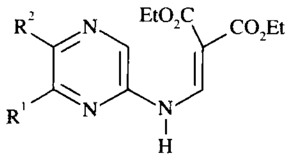
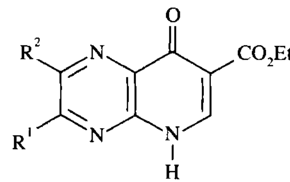
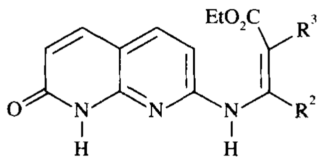
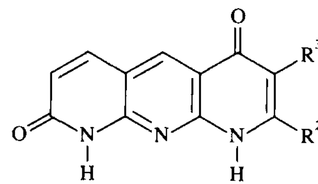
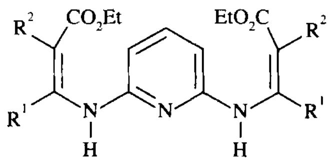
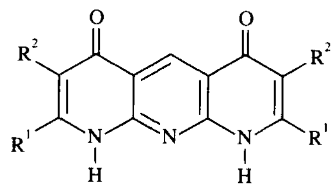
441 **442** **572**

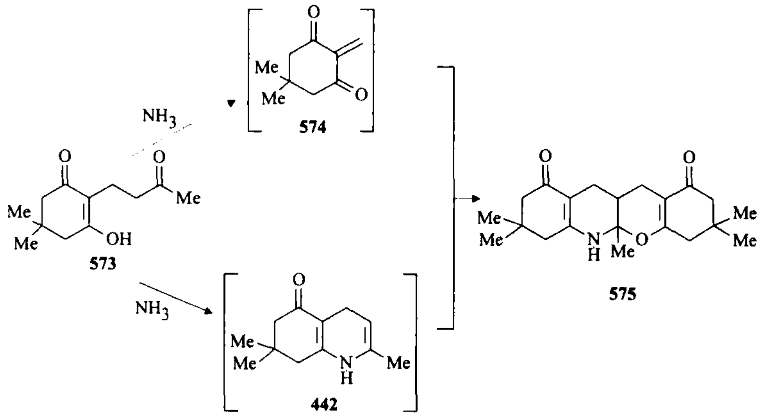
SCHEME 155

TABLE VIII

PYRIDINES FUSED TO SIX-MEMBERED HETEROCYCLES

Entry	Enaminone	Reagents	Product	References
1	 R^1 = H, Me, CO_2Me; R^2 = H, CN, COMe, CO_2Et; R^3 = Me, Et	Dowtherm A		77JHC1009
2	 R^1 = H, Me; R^2 = H, CO_2Me; R^3 = H, CO_2Et	Ph_2O		85JHC89
3	 R = Me, Et	 /DMF		78S691 81JHC607

4	 R^1, R^2 = Et, $PhCH_2$; R^3 = H, $PhCH_2$, $PhCH_2CONH$, $C_6H_4(CO)_2NH$	 /PCl_5		91JCS(P1)3077
5	 R^1 = Me, Me_2N, EtO, MeS, EtS, $(CH_2)_4N$, $(CH_2)_5N$; R^2 = H, Me	Dowtherm A		74CPB1864
6	 R^1 = Me, Ph; R^2 = H, Me; R^3 = H, COMe, CN	Dowtherm A or liquid paraffin		66G103 66G1443 71JCS(C)2991
7	 R^1 = H, Me; R^2 = H, CO_2Et	Dowtherm A		66G103 70JHC875



SCHEME 156

4. *Pyridothiazines*

Michael reaction of thiazine-based enaminones to various acrylates in the presence of phosphorus trichloride followed by ring closure gives pyrido[2,1-*b*][1,3]thiazine derivatives in good yields (Table VIII, entry 4). These pyridothiazines were prepared as analogues of β-lactam antibiotics.

5. *Pyridopyrazines*

Pyrido[2,3]pyrazines can be prepared by thermal cyclization of enaminones derived from 2-aminopyrazines (Table VIII, entry 5).

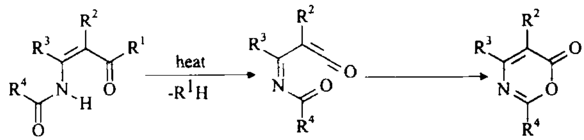
6. *Anthyridines*

Anthyridines are prepared in moderate yields by thermal cyclization of enaminones derived from 2-amino-1,8-naphthyridines (Table VIII, entry 6), or from dienaminones derived from 2,6-diaminopyridine (Table VIII, entry 7).

J. OXAZINES AND OXAZINONES

1,3-Oxazin-6-ones **578** can generally be prepared, via the ketene intermediates **577**, by intramolecular cyclizations of *N*-acyl enaminones **576** at elevated temperature, Scheme 157 (63N403; 72AGE128; 74AGE533; 75JA6590; 80LA798). Thermolysis of oxazolin-5-ones **579** to 1,3-oxazin-6-

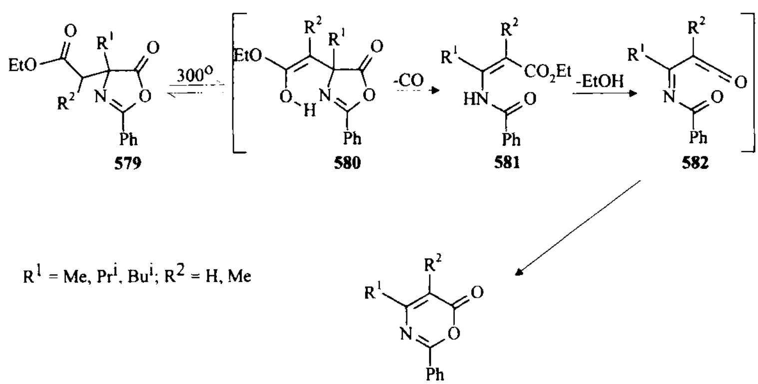
ones **583** also involves the *N*-acyl enaminones **581** and the ketene intermediates **582** by elimination of carbon monoxide and ethanol, Scheme 158 (76CB2327).



576 577 578

R^1 = H, OMe, OEt; R^2 = H, Me, Ph; R^3 = H, Me; R^4 = H, alkyl, OEt

SCHEME 157

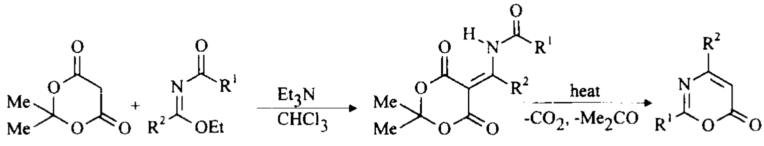


579 580 581 582 583

R^1 = Me, Pr^i, Bu^i; R^2 = H, Me

SCHEME 158

Reaction of Meldrum's acid **584** with the acylimidates **585** gives the enaminones **586** in good yields. Mild heating of **586** causes loss of acetone and carbon dioxide and affords the 1,3-oxazin-6-ones **587** in 33–93% yields, Scheme 159 (86CPB1980).

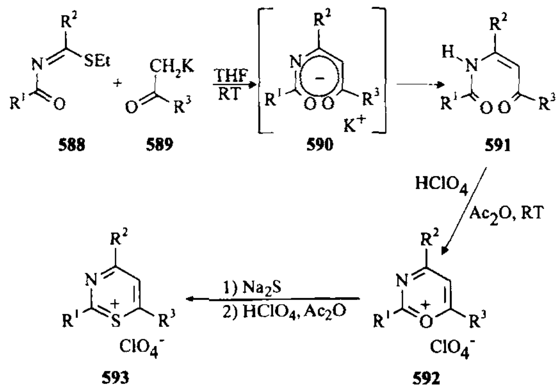


584 585 586 587

R^1 = Me, Et, Pr^i, Bu^t, Ph, $PhCH_2$; R^2 = Me, Ph

SCHEME 159

Reaction of the *N*-(substituted)thiocarbonimidates **588** with the potassium enolate of methyl ketones **589** gives the *N*-acyl enaminones **591** in moderate to good yields. The use of two equivalents of potassium *t*-butoxide suppresses side reactions by generation of the intermediate salt **590** and facilitates the isolation of **591.** The enaminones **591** undergo ring closure to the 1,3-oxazinium salts **592** on treatment with perchloric acid. Treatment of **592** with sodium sulfide followed by perchloric acid gives the corresponding 1,3-thiazinium salts **593,** Scheme 160 (83JOC623).

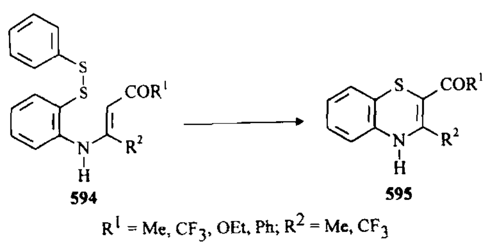


R^1 = 2,5-$Cl_2C_6H_3$, 2-C_4H_3O; R^2 = SEt, NEt_2; R^3 = Ph, 2-HSC_6H_4, 4-$MeOC_6H_4$

SCHEME 160

K. BENZOTHIAZINES AND PHENOTHIAZINES

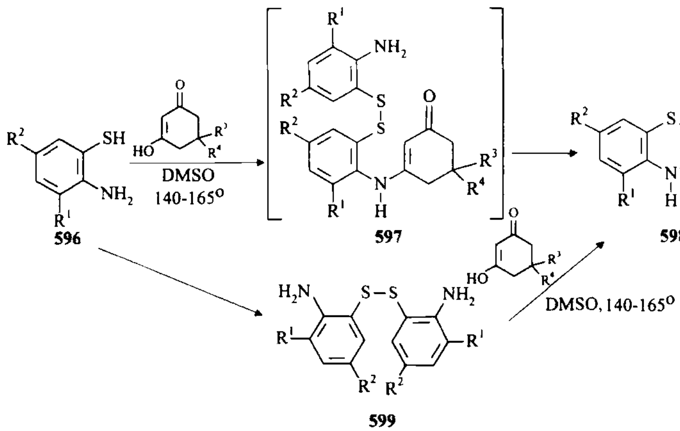
Miyano and co-workers [75JCS(CC)760; 76JCS(P1)1146] and subsequently other groups (80TL3795; 83S933) reported that reactions between *o*-thioaniline and 1,3-dicarbonyl compounds in DMSO give the enaminones **594,** which cyclize to the benzothiazines **595** in good yields, Scheme 161.



R^1 = Me, CF_3, OEt, Ph; R^2 = Me, CF_3

SCHEME 161

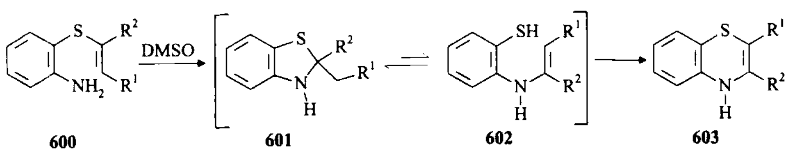
Similar condensations of *o*-thioanilines **596** with cyclohexane-1,3-diones probably give intermediates **597**, which spontaneously cyclize to the phenothiazines **598** in good yields, Scheme 162 [75JCS(CC)760; 76JCS(P1)1146; 80TL3795; 83S933]. The rationale for the involvement of the disulfide intermediates was based on the known ready oxidation of compounds **596** to disulfides **599** (63JOC3246), which were treated with cyclohexanediones to give **598**.



R^1 = H, NO_2; R^2 = H, Cl, OMe; R^3 = H, Me; R^4 = H, Me, Ph

SCHEME 162

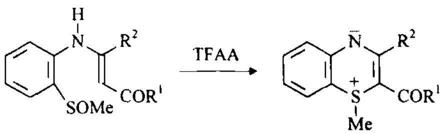
In the conversion of the vinyl thioethers **600** to the benzothiazines **603**, the benzothiazolines **601** are in equilibrium with the intermediate enaminones **602**, Scheme 163 (80JHC793).



R^1 = CO_2Me, CO_2Et, CN; R^2 = H, Ph

SCHEME 163

2-Methylsulfinylaniline gives the enaminones **604,** which cyclodehydrate on treatment with trifluoroacetic anhydride to the benthothiazine ylides **605,** Scheme 164. Enaminones **604** may also be made from 2-methylthioaniline and 1,3-dicarbonyl compounds followed by oxidation [82JCS(P1)831; 85HCA2216]. The ylides **605** are readily demethylated in hydrochloric acid to give the corresponding benthothiazines [82JCS(P1)831].



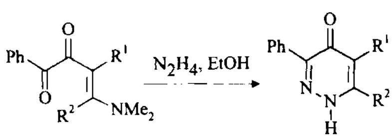
604 **605**

R^1 = Ph, OMe, OEt; R^2 = Ph, OMe

SCHEME 164

L. PYRIDAZINES

Enaminones **606** are treated with hydrazine to give 4-pyridazinones **607,** Scheme 165 (79S385).



606 **607**

R^1 = H, Me, Ph; R^2 = H, Me

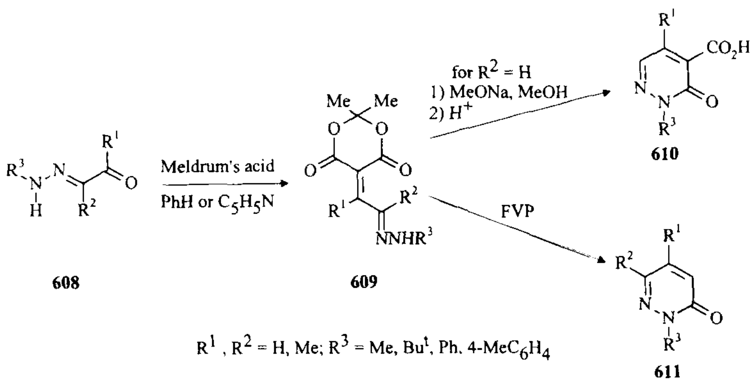
SCHEME 165

Knoevenagel reactions of azaenaminones **608** with Meldrum's acid give the azadienaminones **609,** which undergo either base-catalyzed cyclization to the 3-oxopyridazin-4-carboxyxlic acids **610** or flash vacuum pyrolysis to the pyridazin-3-ones **611,** Scheme 166 [82JCS(P1)1845].

M. PYRIMIDINES AND THEIR DERIVATIVES

1. *Pyrimidines*

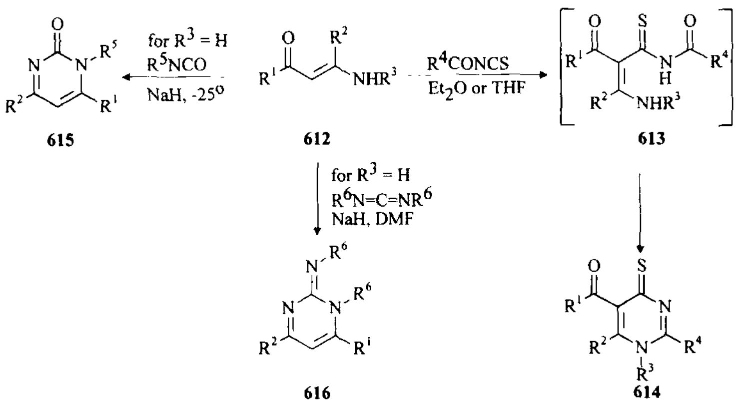
4-Thiopyrimidines **614** are prepared by reactions of enaminones **612** with acyl isothiocyanates via intermediates **613,** Scheme 167 (64JOC1115, 64JOC2887; 65CB1531; 70TL3957; 82S65). The reaction is quite general,



R^1, R^2 = H, Me; R^3 = Me, Bu^t, Ph, 4-MeC_6H_4

SCHEME 166

but usually gives higher yields when R^4 is an electron-withdrawing group. The reaction can be adjusted to prepare 2-oxo- or 2-thiopyrimidines **615** (83S151) and 2-iminopyrimidines **616** (83S409).

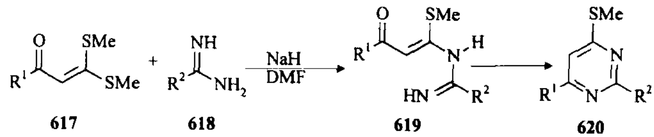


R^1 = alkyl, aryl, EtO; R^2 = alkyl, aryl, NH_2; R^3 = H, alkyl; R^4, R^5 = alkyl, aryl; R^6 = aryl

SCHEME 167

The reactions of α-oxoketene dithioacetals with amidines, guanidines, and isothioureas constitute a general preparation of substituted pyrimidines via enaminone intermediates. A ketene dithioacetal **617** reacts with an amidine, a guanidine, or a thiourea **618** in the presence of sodium hydride to give an enaminone intermediate **619,** which cyclizes to a 4-methylthiopyrimidine **620** in moderate to good yield, Scheme 168 (74CPB2246, 74S880;

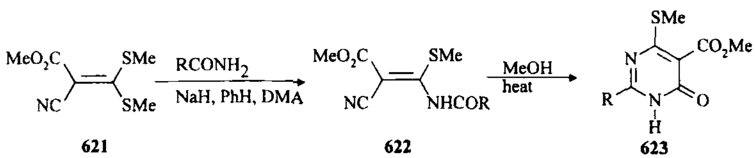
76T1779; 78JPR576; 79T551; 83JOC4841). In the presence of a sodium alkoxide, however, the 4-methylthio group is replaced by an alkoxy group to give **620** (SMe replaced by OMe, OEt, or OPr) (74S880; 76T1779, 76T1911; 78JPR576; 79T551; 83JOC4841).



R^1 = alkyl, aryl; R^2 = alkyl, aryl, NH_2, SH; R^3 = Me, Et

SCHEME 168

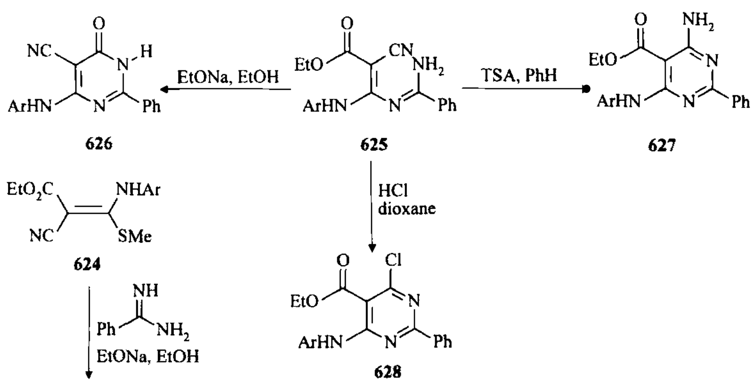
The ketene dithioacetal **621** gives the *N*-acyl enaminones **622,** which readily cyclize to the pyrimidones **623,** Scheme 169 (83H1745; 88JHC959).



R = Me, $ClCH_2$, aryl

SCHEME 169

Displacement of the methylthio group in the enaminone **624** with benzamidine gives the intermediate **625,** which can be isolated. Under basic conditions, **625** cyclizes to the pyrimidone **626,** but in acid, attack on the

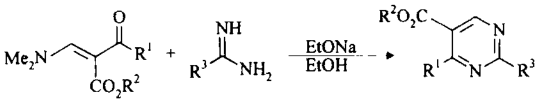


Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4

SCHEME 170

nitrile group gives the pyrimidine **627.** When hydrochloric acid was used, a nucleophilic displacement of $-NH_2$ by chloride was thought to account for the formation of **628,** Scheme 170 (84TL1291).

Condensation of the enaminone **629** with guanidine (**630,** $R^3 = NH_2$), acetamidine (**630,** R^3 = Me), or benzamidine (**630,** R^3 = Ph) in base gives the pyrimidine derivatives **631** in 60–88% yields, Scheme 171 (90JHC295).

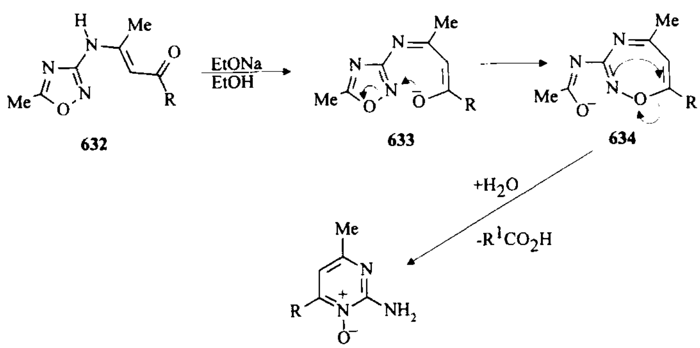


R^1 = alkyl, aryl; R^2 = Me, Et; $R^3 = NH_2$, Me, Ph

SCHEME 171

2. *Pyrimidine-N-Oxides*

The *N*-(1,2,4-oxadiazol-3-yl)-enaminone **632** has two nucleophilic sites in its enaminone chain theoretically capable of attacking N-2 of the oxadiazole ring in a mononuclear heterocyclic rearrangement reaction (i.e., the central carbon as a carbanion and the carbonyl oxygen atom as an enolate). On reflux with an equimolar amount of sodium ethoxide in ethanol, the enolate anion in the intermediate **633** attacks the nitrogen atom to give the intermediate **634,** which undergoes ring contraction and hydrolysis of the acylamino group to give the pyrimidine-*N*-oxide **635,** Scheme 172 [86JCS(P1)17].

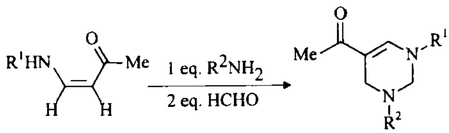


R = Me, Ph

SCHEME 172

3. *Hydropyrimidines*

Condensation of the enaminone **636** with one equivalent of a primary amine and two equivalents of formaldehyde readily gives the tetrahydropyrimidines **637** in moderate yields, Scheme 173 (81AP767).

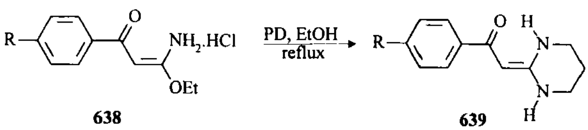


636 **637**

R^1 = Me, Ph, $PhCH_2$; R^2 = Me, Bu^t

SCHEME 173

Enaminones **638** condense with 1,3-propanediamine (PD) to give hexahydropyrimidines **639**, Scheme 174. The products were shown to exist in solution exclusively as the conjugated enaminones stabilized by the intramolecular hydrogen bonds (87S357).



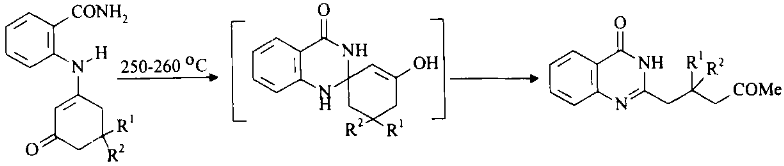
638 **639**

R = H, Cl, Br, MeO

SCHEME 174

N. QUINAZOLINES

A ready preparation of the 4(3*H*)-quinazolone **642** by fusion of the enaminone **640** was assumed to involve the intermediate **641**, Scheme 175 (83S401).

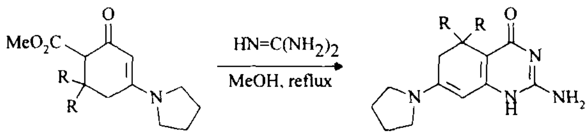


640 **641** **642**

R^1 = H, Me; R^2 = H, Me, Ph

SCHEME 175

Condensations of the enaminones **643** with guanidine give the quinazolone derivatives **644** in good yields, Scheme 176. Hydrogenation of **644** (R = Me) saturated the 7,8 double bond (92JHC1375).



643 **644**

R = H, Me

SCHEME 176

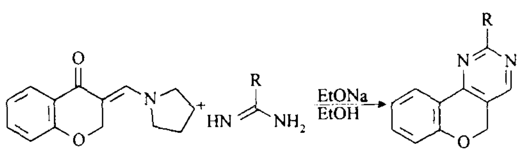
O. PYRIMIDINES FUSED TO OTHER HETEROCYCLES

1. *Thiazolopyrimidines*

Thiazolo- and benzothiazolopyrimidines are generally prepared by thermal cyclization of the enaminones prepared from 2-aminothiazoles and 2-aminobenzothiazoles with diethyl ethoxymethylenemalonate (Table IX). Two methods have been employed. Method A is a one-pot reaction of aminothiazoles with malonate in refluxing 1,2,4-trichlorobenzene without isolation of the enaminone intermediates. In method B, isolation of the enaminone intermediates prior to cyclization in trichlorobenzene usually provides purer products (72JMC1203).

2. *Benzopyranopyrimidines*

Benzopyrano[3,4-*d*]pyrimidines **646** were reported to be prepared by the reaction of enaminone **645** with amidines or guanidine under basic conditions, Scheme 177 (86JHC1753).



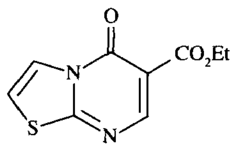
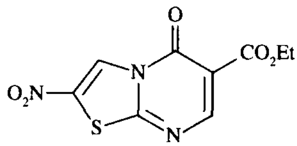
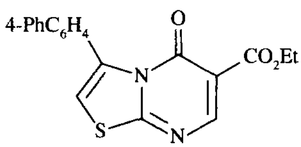
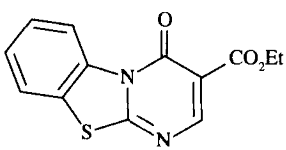
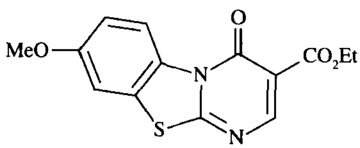
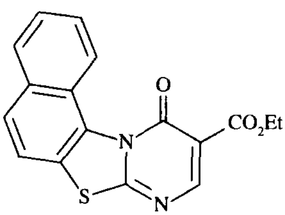
645 **646**

R = H, Me, Ph, NH_2

SCHEME 177

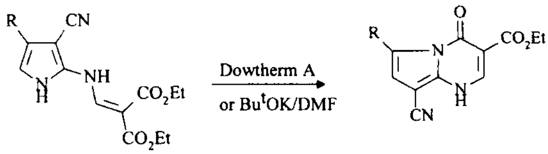
TABLE IX

THIAZOLOPYRIMIDINES

Entry	Thiazolopyrimidine	Method	Yield (%)
1		B	78
2		A	33
3		A B	29 53
4		A B	49 28
5		B	76
6		A	63

3. *Pyrrolopyrimidines and Pyrazolopyrimidines*

4-Oxopyrrolo[1,2-*a*]pyrimidine derivatives **648** are prepared by either thermal or base-catalyzed cyclization of the enaminones **647**, Scheme 178 (87JHC297).

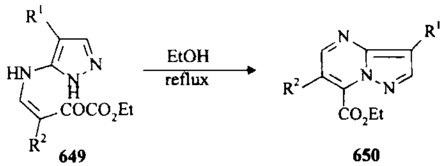


647 648

R = Ph, 4-FC_6H_4

SCHEME 178

Enaminones **649** are cyclized in ethanol to give the pyrazolo[1,5-*a*] pyrimidines **650** in moderate yields, Scheme 179 (79H397; 81JHC163).



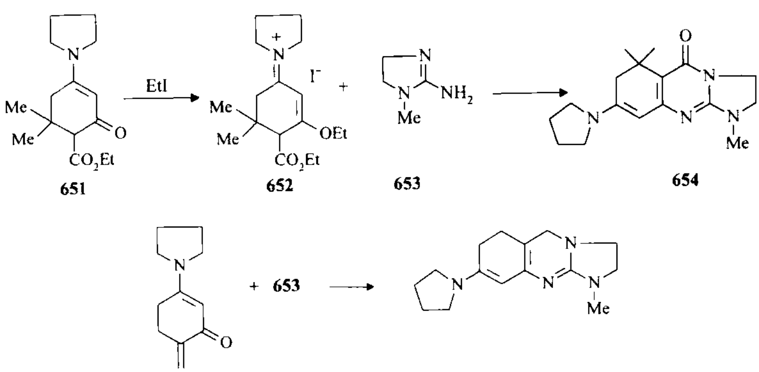
649 650

R^1 = CN, CONHMe, $CONH_2$; R^2 = COMe, CO_2Et

SCHEME 179

4. *Imidazoloquinazolines*

Treatment of the enaminone **651** with iodoethane gives the salt **652,** which readily condenses with 2-amino-1-methylimidazoline **653** to give the imidazolquinazolinone **654.** The same imidazoline adds to the enaminone **655** to give **656,** Scheme 180 (92JHC1375).



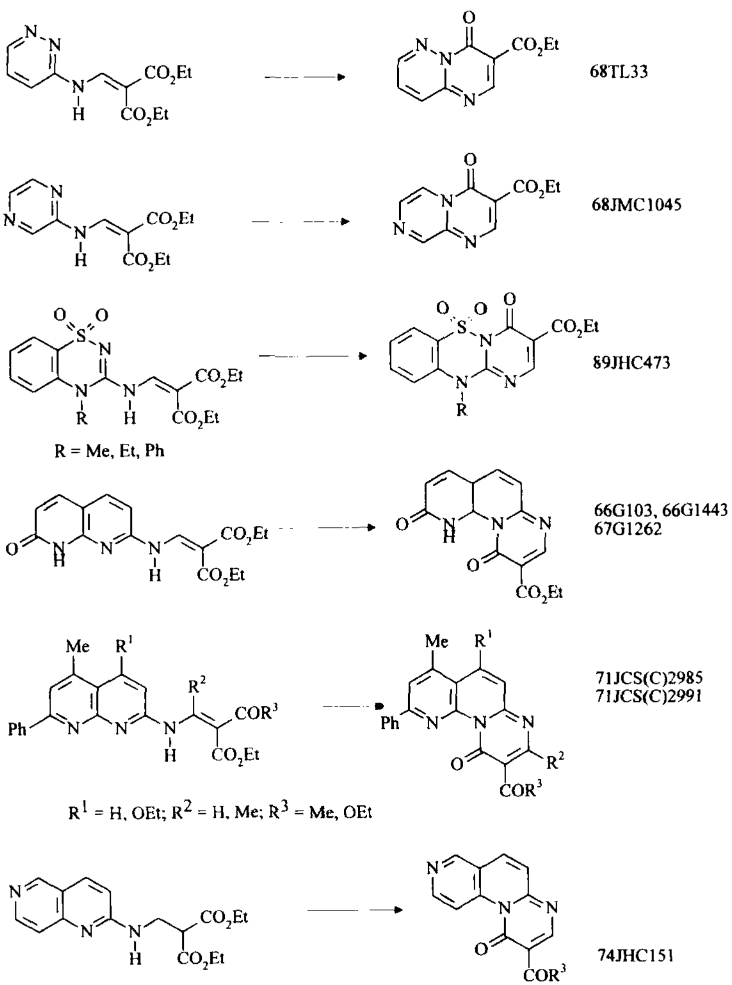
651 652 653 654

655 656

SCHEME 180

5. *Other Pyrimidines Fused to Six-Membered Heterocycles*

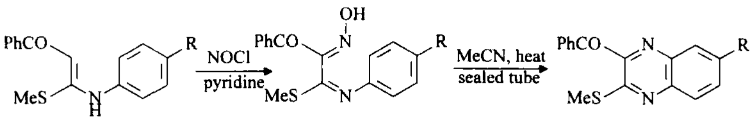
Enaminones derived from aminodiazines and ethoxymethylenemalonates often ring-close onto a ring nitrogen atom to give fused pyrimidines; examples are shown in Scheme 181. In every case reaction is effected in Dowtherm A at high temperature.



SCHEME 181

P. Quinoxalines

Treatment of the enaminones **657** with nitrosyl chloride gives the hydroxyiminoimines **658,** which are heated in sealed tubes to give the quinoxalines **659** in good yields, Scheme 182 [84JCS(CC)430].

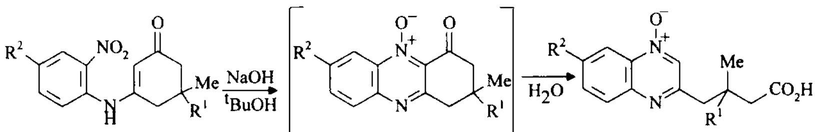


657 **658** **659**

R = H, Cl

Scheme 182

The enaminones **660** were refluxed with sodium hydroxide to give the quinoxaline *N*-oxides **662** in excellent yields. Since α-acyl aromatic-*N*-oxides are readily hydrolyzed under basic conditions, the *N*-oxide **661** was suggested as the intermediate, Scheme 183 (81S60).



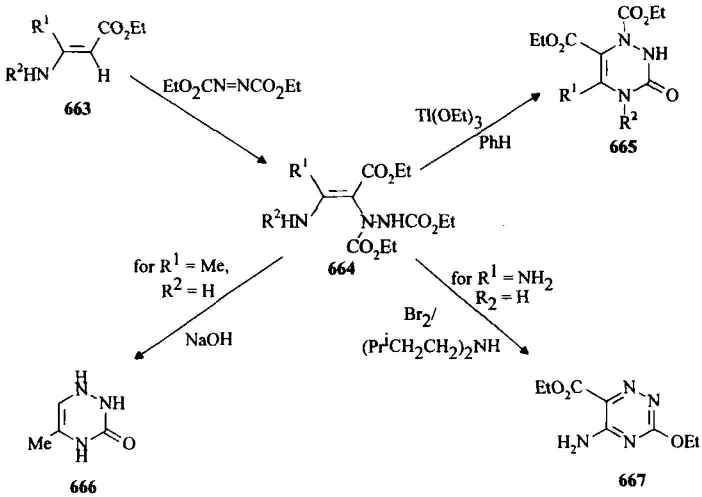
660 **661** **662**

R^1 = H, Me; R^2 = H, Me, OMe

Scheme 183

Q. Triazines

Taylor and co-workers found that the Michael additions of diethyl azodicarboxylate to the enaminones **663** gave the derivatives **664,** which were cyclized with thallium ethoxide to the *as*-triazinones **665** in almost quantitative yields. Cyclization of **664** was also effected with aqueous sodium hydroxide, but under these conditions concomitant hydrolysis and decarboxylation occurred to give the triazinone **666.** The cyclization of the enaminone **664** (R^1 = NH_2, R^2 = H) failed under basic conditions, but treatment with bromine and diisopropylethylamine smoothly afforded the triazine **667,** Scheme 184 (70JOC3792).



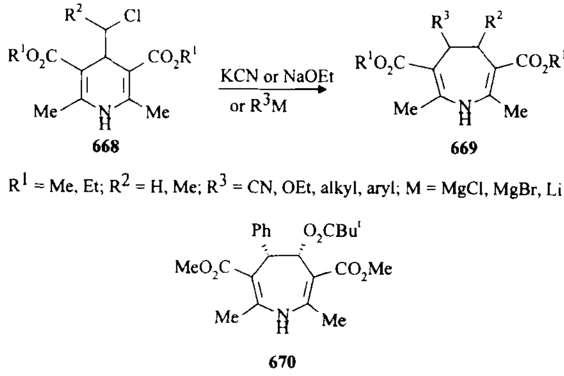
R^1 = H, Me, NH_2; R^2 = H, Me

SCHEME 184

VII. Seven-Membered Rings

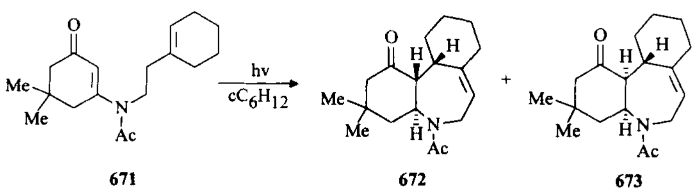
A. AZEPINES

Base-catalyzed ring expansion–nucleophilic additions to the enaminones **668** (dihydropyridine derivatives) are useful in the preparation of azepine derivatives. Thus, treatment with potassium cyanide or sodium ethoxide gives the azepine derivatives **669** (R^3 = H) (63JCS4819; 65JCS2411). This procedure was extended to the use of Grignard or lithium reagents to give the azepines **669** with a variety of substituents in good to excellent yields, Scheme 185 (84JOC3871). Of the organometallics studied, the Grignard reagents appear to be the best in terms of yield and convenience. The aryl Grignard reagents give stereoselectively the cis addition products (>10 : 1) and the alkyl reagents give the trans products (>15 : 1). This was used in the stereoselective synthesis of the azepine **670** (85% yield, 98% ee).



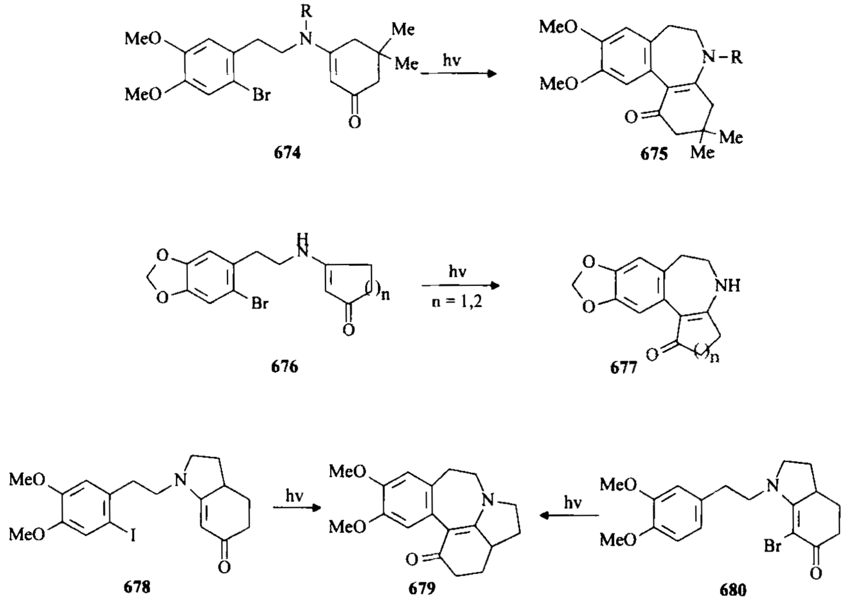
SCHEME 185

The Pyrex-filtered irradiation of the enaminone **671** gives an intramolecular ene reaction rather than a 2 + 2 cycloaddition to produce a steroisomeric mixture, **672** and **673,** Scheme 186 (78JOC4420).



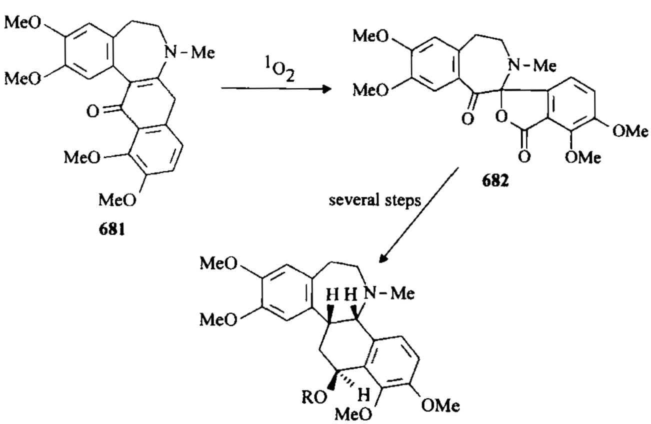
SCHEME 186

Photocyclizations of *N*-haloarylalkyl-substituted enaminones have often been employed in the synthesis of azepines. Irradiation of the enaminones **674** at wavelengths > 300 nm afforded the azepines **675** in excellent yields (91–94%) (78TL3817). Irradiation at wavelengths > 200 nm converted the enaminones **676** to azepines **677** in 50–85% yields with only traces of side products (82JOC482). The halogenated enaminones **678** and **680** were irradiated at wavelengths above 300 nm to give the tetracyclic azepine **679** in 50 and 38% yields, respectively. Scheme 187 [77JCS(CC)644; 78JOC975; 79JOC1074]. Similar compounds have been prepared by anodic intramolecular cyclizations (84TL5023).



SCHEME 187

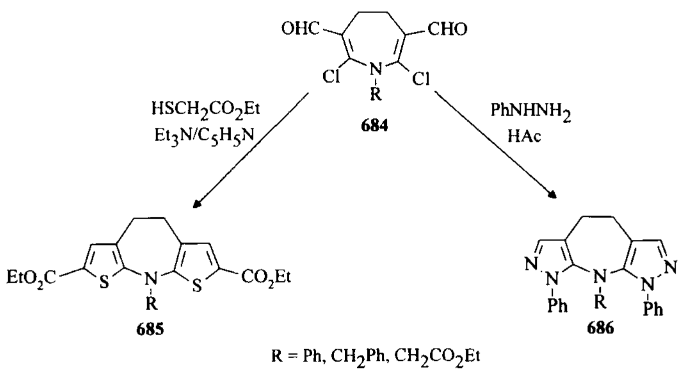
A photosensitized oxidation of the enaminone **681** using singlet oxygen was used in the total synthesis of the alkaloids Alpinigenine (**683a**) and Alpinine (**683b**). The oxidation takes place on the enaminone double bond followed by a sequential ring opening–ring closing to the intermediate **682,** Scheme 188 (74JA1944).



683 a, R = H; **b**, R = Me

SCHEME 188

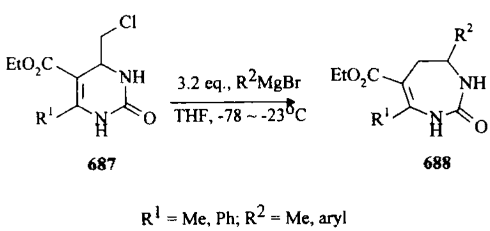
The cyclic enaminones **684** condense with ethyl 2-mercaptoacetate to give the dithieno[*b,f*]azepines **685** and with phenylhydrazine to give the dipyrazolo[*b,f*]azepines **686**, Scheme 189 [89JCS(P1)2095].



SCHEME 189

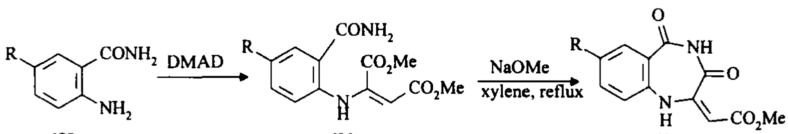
B. DIAZEPINES

Treatment of the enaminones **687** and three equivalents of a Grignard reagent at low temperatures gives the diazepine derivatives **688** in excellent yields, Scheme 190. The reaction mechanism was assumed to be initiated by deprotonation at N-1 followed by elimination of chlorine to form a cyclopropane intermediate and addition of the Grignard reagent. Evidence for this mechanism was provided by the failure of the N-1 methyl derivative of **687** to react under similar conditions (86S664).



SCHEME 190

Anthranilamides **689** were found to react with dimethyl acetylenedicarboxylate to give the enaminones **690,** which ring-closed under basic catalysis to the benzodiazepinediones **691,** Scheme 191 (68JOC3997).

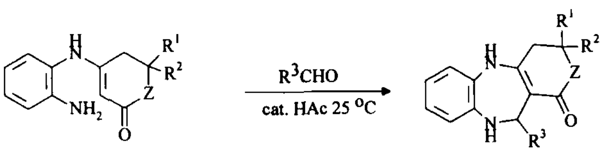


689 **690** **691**

R = H, Me, Cl, Br

SCHEME 191

Mannich reactions of the enaminones **692** with aldehydes under mild conditions give the benzodiazepine derivatives **693** in high yields, Scheme 192 (72CPB1588; 90SC1579).



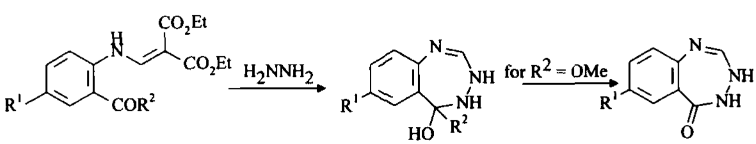
692 **693**

R^1, R^2 = H, Me; R^3 = H, alkyl, aryl; Z = O, CH_2

SCHEME 192

C. TRIAZEPINES

Benzotriazepines **695** and benzotriazepinones **696** are reported to be synthesized by condensations of the enaminones **694** with hydrazine hydrate, Scheme 193 (69CJC489).



694 **695** **696**

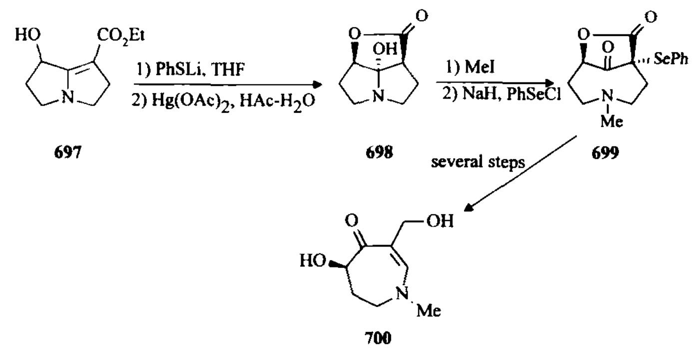
R^1 = H, Cl, NO_2; R^2 = OMe, aryl

SCHEME 193

VIII. Eight-Membered Rings

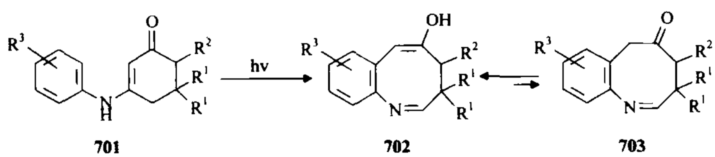
A. Azocines

Michael addition of lithium thiophenolate to the enaminone **697** followed by treatment with mercuric acetate gives the hydroxy lactone **698**. *N*-Methylation followed by base treatment and phenylselenyl chloride provides the azocinone derivative **699**, which has been elaborated on to the alkaloid Otonecine **700**, Scheme 194 (83TL5731).



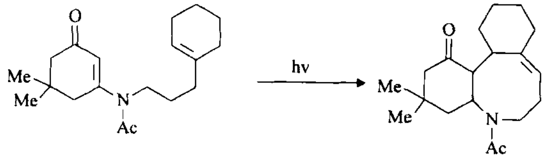
SCHEME 194

Irradiations of the enaminones **701** with a high-pressure mercury lamp give the benzazocine derivatives **702** as major products, Scheme 195. Mechanistic studies suggest that the photocyclization occurs from an enaminone triplet state (*n–p**) and involves several intermediates (72TL2513; 73BCJ2504; 74TL1741). Pyrex-filtered irradiation of the enaminone **704** was found to stimulate an intramolecular ene reaction to give the tricyclic azocine **705**, Scheme 196 (78JOC4420).



R^1, R^2 = H, Me; R^3 = H, OMe, Cl

SCHEME 195



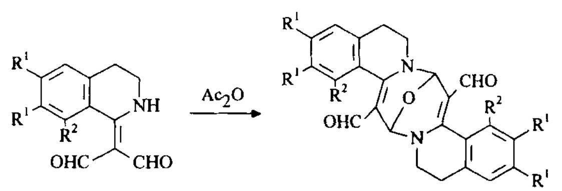
704 705

SCHEME 196

The intramolecular *N*- and *C*-arylation of enaminones with lithium diethylamide was reported to give tricyclic azocines as minor products (79JOC3985).

B. Diazocines

Treatment of the enaminones **706** with acetic anhydride, gave unexpectedly the diazocine derivatives **707,** Scheme 197 (92TL6011). The mechanism was assumed to involve dimerization of **706** to give a bis-carbinolamine, which undergoes dehydration to form the oxygen bridge.



706 707

$R^1, R^2 = H, OMe; R^1R^1 = OCH_2O$

SCHEME 197

IX. Conclusion

The many examples presented here amply demonstrate the versatility and usefulness of enaminones in heterocyclic syntheses, but as alert readers will realize, the chemistry of enaminones is so rich that much of it remains to be explored. Its applications in natural product synthesis, particularly that of alkaloids, and in both nonheterocyclic and heterocyclic syntheses are expected to grow continuously. We hope the present view attracts general interest and stimulates further exploration of this fascinating and important field.

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Synthesis of Quaternary Benzo[*c*]phenanthridine Alkaloids and Their Analogues

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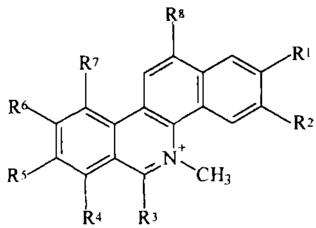
I. Introduction

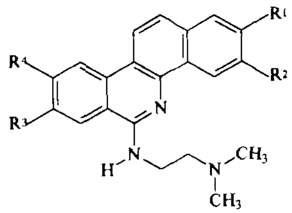
The benzo[*c*]phenanthridine alkaloids are a small group of natural products with very limited distribution in the plant kingdom. Their value to the plants that produce them seems, at least in part, to be attributable to their inhibitory effects on cell division when ingested by a predator, be the predator bacterial, fungal, or mammalian. The pharmacological activities of the benzo[*c*]phenanthridine alkaloids also apply in the main to conditions characterized by rapid cell growth. Sanguinarine **1** and chelerythrine **2** (see Fig. 1) have activity against fungal organisms such as *Candida* and *Trichophyton* (84MI1) and demonstrate significant antibacterial activity, particularly against gram-positive bacteria (81MI1). However, neither possess antitumor activity, tending to be cytotoxic in nature (73JHC85, 73JMC939; 75JMC708). Fagaronine **3** and nitidine **4,** however, have been reviewed as potential antitumor (75JMC708; 81JHC223; 84JMC544, 84JNP453; 87MI1; 88MI1; 89PHA593; 92MI1; 93MI1) and antiviral agents



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	
1	OCH_2O		H	OCH_2O		H	H	H	
2	OCH_2O		H	OCH_3	OCH_3	H	H	H	
3	OH	OCH_3	H	H	OCH_3	OCH_3	H	H	
4	OCH_2O		H	H	OCH_3	OCH_3		H	H
5	OCH_3	OCH_3	H	H	OCH_3	OCH_3	H	H	
6	OCH_3	OH	H	H	OCH_3	OCH_3	H	H	
7	OCH_2O		H	H	OCH_2O		H	H	
8	OCH_3	OCH_3	H	H	OCH_2O		H	H	
9	OCH_2O		CH_3	H	OCH_3	OCH_3	H	H	
10	OCH_2O		H	OCH_3	OCH_3	OCH_3		H	H
11	OCH_2O		H	H	OCH_3	OCH_3	OCH_3	H	
12	OCH_3	OCH_3	H	H	OCH_3	OCH_3		H	OH
13	OCH_2O		H	OCH_3	OCH_3	H	H	OCH_2CH_3	
14	OCH_2O		H	OCH_3	OH	H	H	H	
15	OCH_2O		H	OH	OCH_3	H	H	H	

FIG. 1

(92BBR370, 92TL2275), but do not exhibit the biological activities of sanguinarine or chelerythrine. The elucidation of the mechanism of action through an effect on the topoisomerase (93JOC5025, 93MI2, 93MI3) and reverse transcriptase enzymes (76MI1; 79JNP187; 81MI4; 85JPS889; 87MI2) by binding to DNA (83MI1, 83MI2; 84MI2, 84MI3; 85MI1, 85MI2; 86MI1; 87MI2; 94MI1) renders this group of compounds prime targets for exploitation in chemotherapy, through structural modification, as antineoplastic, antibacterial, antifungal, antiprotozoal, anthelmintic, and antiviral agents. The plethora of synthetic routes makes available almost any desired struc-

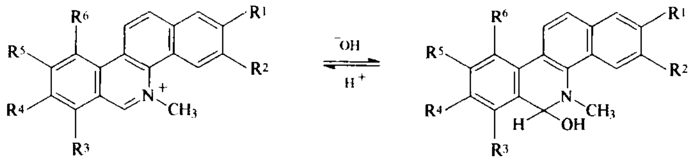


	R^1	R^2	R^3	R^4
16	OCH_3	H	OCH_3	H
17	OCH_2O		OCH_3	OCH_3
18	OCH_3	OCH_3	OCH_3	OCH_3
19	OCH_3	H	OCH_3	H
20	H	OCH_3	H	H

FIG. 1 (*Continued*)

tural analogue (see Section II), yet the number of compounds for which anticancer data have been secured remains surprisingly small. There is, similarly, very little information concerning selectivity of action, other than the early reports of differences between 7,8 and 8,9 oxygen substitution.

In 1979, Caolo and Stermitz [79H(12)11] proposed a chemical property correlation between the substituent pattern of the benzo[*c*]phenanthridines and their biological activity. They noted that the activity dichotomy between the 2,3,8,9-substituted benzo[*c*]phenanthridines fagaronine and nitidine, which were active against the P388 and L1210 cell lines, and the inactive sanguinarine and chelerythrine (2,3,7,8-substituted) extended to other areas. The latter alkaloids exhibited antifungal, antibacterial, anti-inflammatory (81MI1), and anti-Na, K-ATPase (81MI2) activity, whereas the former did not. They noted that in terms of the equilibrium that exists between the iminium ion form and the neutral alkanolamine in aqueous solutions (Scheme 1), both sanguinarine and chelerythrine formed the alkanolamine at a lower pH than the 2,3,8,9-substituted benzo[*c*]phenanthridines and were more sensitive to the attack of the OH^- anion. They proposed that a prerequisite for antitumor activity was the tendency for the alkaloid to be present almost exclusively as the iminium ion at physiological pH. They surmised that an alkoxy substituent in position 7 was instrumental in shifting the equilibrium in favor of the alkanolamine through steric interaction with the *peri*-H at position 6, destabilizing the iminium ion form.



SCHEME 1

In addition, resonance interaction of the oxygen lone pair from a substituent in position 9 with the iminium double bond would stabilize the iminium ion form through the *para*-quinoid structure. Resonance interaction is also possible with an oxygenated substituent at position 7, although the resultant *ortho*-quinoid structure would not make as significant a contribution to stabilization as the para form [79H(12)11]. Examples of the wide variety of benzo[*c*]phenanthridines that have been assessed for biological activity are shown in Fig. 1. A systematic study of structure–activity relationships would be of great interest, particularly if it were possible to couple this with crystallographic and NMR studies and molecular modeling of the drug–DNA complex; of greater interest would be a study of the drug–DNA–topoisomerase complex, which is assumed to account for the observed effects. The demonstration of the potent antimalarial activity of nitidine *in vitro* (95AAC2606) opens a new area of inquiry, specifically whether there is any scope for separation of antimalarial from cytotoxic activity.

II. Synthesis of Quaternary Benzo[*c*]phenanthridines

The scope of this synthetic review applies to the known quaternary benzo[*c*]phenanthridine alkaloids and their analogues, which have been synthesized to develop new pharmacologically active agents. The applicability of the method for producing benzo[*c*]phenanthridines with different oxygenated substitution patterns in ring D of the tetracyclic aromatic nucleus (e.g., 2,3,8,9, 2,3,7,8, or 2,3,7,8,10 substituents) is also assessed, along with the strategies (if any) that have been employed to overcome any shortfalls. The generally accepted numbering of the benzo[*c*]phenanthridine ring system is shown in Fig. 2, along with the alphabetical notation of the individual rings.

The approaches to the synthesis of the benzo[*c*]phenanthridines have focused on two basic strategies: the final formation of ring C or ring B, the former being the more exploited route. This review is also approached from the same angle.

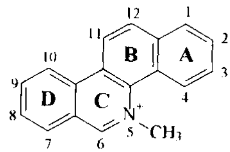


FIG. 2

The formation of ring C (Section II,A) can be further subdivided in terms of the intermediate synthesized as the precursor to final ring construction. One strategy relies on a 2-aryl-1-tetralone intermediate (providing rings A, B, and D) with various methods for introducing the required C—N fragment for ring C (Fig. 3a; Section II,A,1). Alternatively, naphthalene analogues have been used as the key intermediate (providing rings A and B) and reacted with appropriately *ortho*-functionalized aryl analogues (ring D) to enable ring C formation in one or more steps (Fig. 3b; Section II,A,2).

Formation of ring B as the final step has generally proceeded via a 3-arylisoquinoline intermediate to provide rings A, C, and D (Fig. 3c; Section II,B,1). The two-carbon fragment necessary for ring B has either been introduced separately, or already is a functionality of the intermediate, either in the ortho (2-C′) position of the 3-aryl moiety or the 4 position of the isoquinoline. Alternatively, the isoquinoline moiety alone has been viewed as the key intermediate, with rings B and A formed in one step by reaction with the appropriate aryl (ring A) group (Fig. 3d; Section II,B,2).

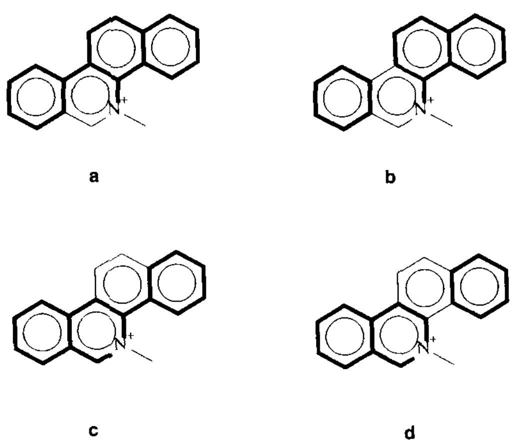


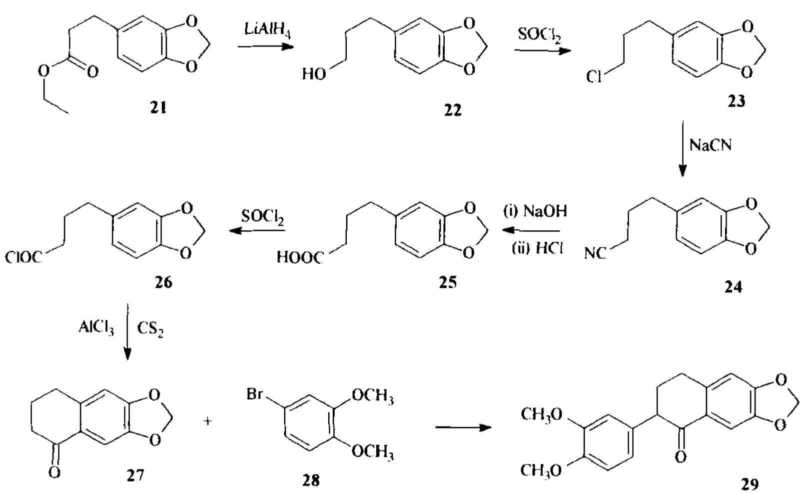
FIG. 3

A. Final Cyclization of Ring C

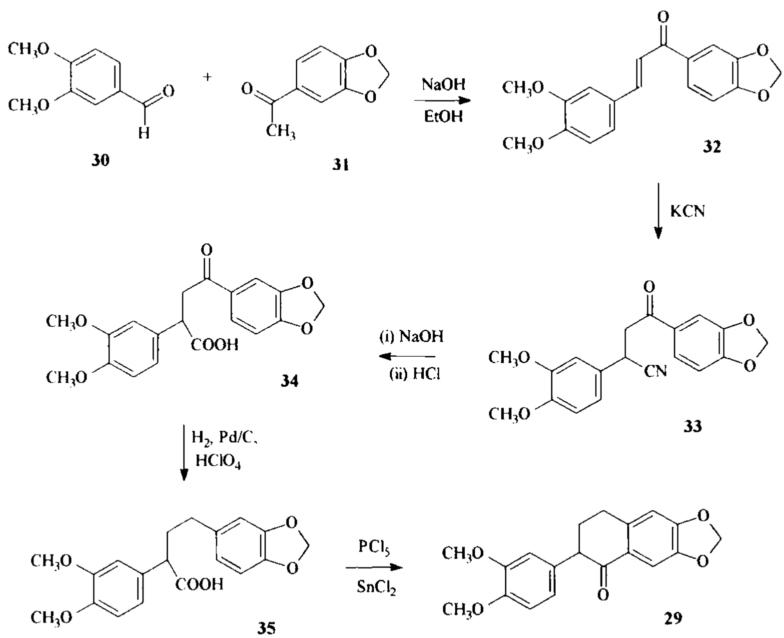
1. *Synthesis via the 2-Aryl-1-tetralone Intermediate*

A common intermediate in the synthesis of benzo[*c*]phenanthridines is the 2-aryl-1-tetralone, which provides rings A, B, and D of the alkaloid nucleus. In 1973, two independent research groups reported the synthesis of nitidine via the 3,4-dihydro-2-(3,4-dimethoxyphenyl)-6,7-methylenedioxy-(2*H*)-naphthalone **29** (Scheme 2). The synthesis of this intermediate was arrived at by two different routes. Kametani *et al.* (73JHC31) reduced 3-(3,4-methylenedioxyphenyl)proprionate **21** to the corresponding alcohol **22** with lithium aluminium hydride, which was then converted to the chloride **23** with thionyl chloride. After production of the nitrile **24** by reaction with sodium cyanide and subsequent hydrolysis to the carboxylic acid **25,** Friedel–Crafts cyclization of the acid chloride **26** afforded the tetralone intermediate **27.** Reaction with 1-bromo-3,4-dimethoxybenzene **28** in the presence of sodium amide yielded the tetralone intermediate **29** in an overall yield of 4%.

To arrive at the 2-aryl-1-tetralone, Zee-Cheng and Cheng (73JHC85, 73JHC867) used the Claisen–Schmidt aldol condensation of veratraldehyde **30** and acetopiperone **31** to produce (3′,4′-methylenedioxy)-3,4-dimethoxychalcone **32** quantitatively (Scheme 3). On addition of hydrogen cyanide the cyanoketone **33** was formed, which after basic hydrolysis and



Scheme 2

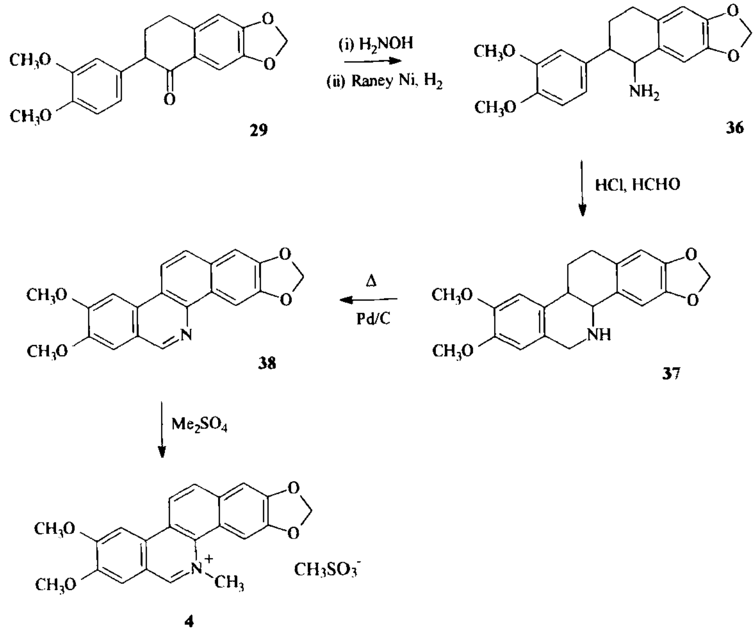


SCHEME 3

subsequent acidification yielded the γ-oxobutyric acid **34.** After catalytic hydrogenation to the butyric acid **35** using Pd/C, cyclization using phosphorus pentachloride gave the tetralone intermediate **29** (Scheme 3). Of the two methods described, Zee-Cheng and Cheng's produced the 2-aryl-1-tetralone in an overall higher yield (67%).

The two groups used different approaches for the construction of ring C in order to produce the target aromatic benzo[*c*]phenanthridines. Kametani *et al.* converted the 2-aryltetralone **29** to the homologous amine **36** by reduction of the oxime intermediate (Scheme 4). Reaction of this amine with acidified formaldehyde under Pictet–Spengler conditions gave the hexahydrobenzo[*c*]phenanthridine **37,** which was dehydrogenated with 30% palladium–charcoal to produce nor-nitidine **38** and quaternized with dimethyl sulfate to the 2,3,8,9 oxygenated benzo[*c*]phenanthridine nitidine **4** in 0.5% overall yield (12% from the 2-aryltetralone).

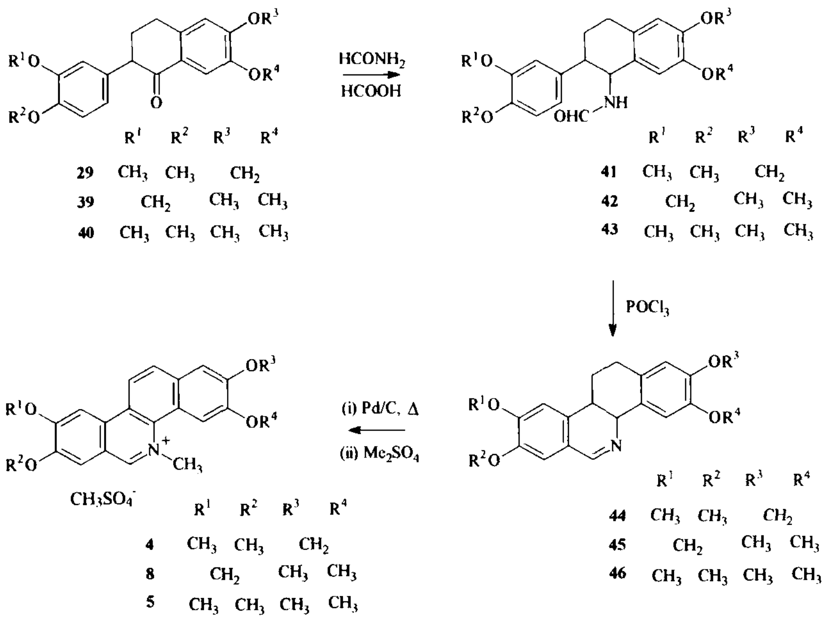
Zee-Cheng and Cheng's (73JHC85; 73JHC867) route to the benzo[*c*]phenanthridines utilized the formation of the *N*-formamide derivatives **41–43** from the corresponding tetralone intermediates **29,39,40** by addition of formamide and formic acid under Leuckart conditions. The derivatives



SCHEME 4

were then cyclized to the tetrahydrobenzo[*c*]phenanthridines **44–46** by the Bischler–Napieralski method using phosphorus oxychloride (Scheme 5). Aromatization and quaternization to afford nitidine methyl sulfate were achieved using the conditions described earlier in Kametani's method (17% overall yield). The alteration of the substituent pattern on the aldehyde and ketone precursors used in the initial aldol condensation allowed the production of the suitable tetralone intermediates **39,40** for synthesizing the two benzo[*c*]phenanthridines alkaloids allonitidine **8** and *O*-methylfagaronine **5** in 14% yields.

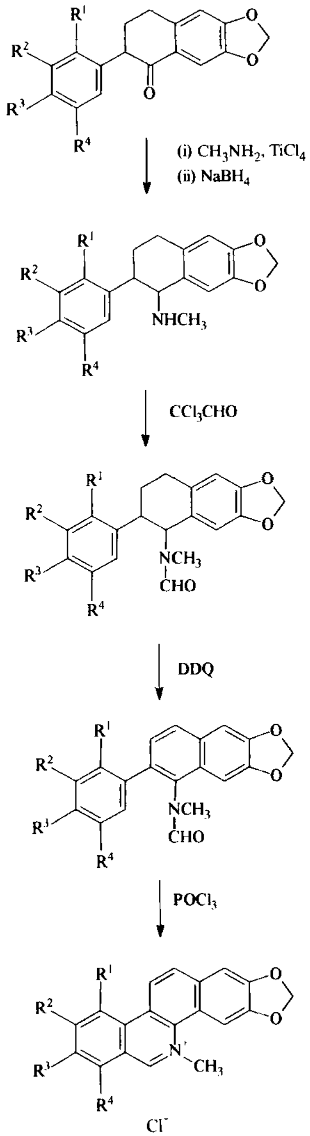
Ishii *et al.* (83CPB3024) have also used the 2-aryl-1-tetralone intermediate as a strategy for producing a number of benzo[*c*]phenanthridines. With the view to using the aldol condensation employed by Zee-Cheng and Cheng as the first step (Scheme 3) to the 2-aryl-1-tetralone intermediate, they synthesized a number of benzaldehyde derivatives to be condensed with 3,4-methylenedioxyacetophenone **31.** Subsequent steps (83CPB3039; 85CPB4139) led to nonphenolic benzo[*c*]phenanthridines with substituent patterns in ring D determined by the benzaldehyde used at the start of the synthetic pathway (Scheme 6). Under conditions used by Zee-Cheng and Cheng (73JHC85, 73JHC867; 75JMC66), the butyric acid derivatives were



SCHEME 5

produced and cyclized to the 2-arytetralone intermediates (**29,47–49**) using phosphorus oxychloride. A more direct route to the quaternary aromatic benzo[*c*]phenanthridine was accomplished by aromatizing ring B prior to construction of ring C (85CPB4139). Reaction of the tetralone intermediates with methylamine in the presence of titanium tetrachloride produced the enamines, which were reduced to the corresponding *N*-methyltetrahydronaphthylamines **50–53** with sodium borohydride. Formylation of the *N*-methyl naphthylamines **54–57** was achieved using chloral, and the amides were then dehydrogenated to the aromatic *N*-methylnaphthylformamides **58–61** using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Bischler–Napieralski cyclization to the quaternary benzo[*c*]phenanthridines (**4,7,10,62**) was achieved using phosphorus oxychloride in acetonitrile (Scheme 6) in yields of 40–69% with respect to the 2-aryltetralone precursors.

Ishii *et al.* found that the sequence developed by Zee-Cheng and Cheng had limited applicability to the synthesis of benzo[*c*]phenanthridines with a 7,8,10 oxygenated substituent pattern in ring D, such as the cytotoxic alkaloids chelilutine **71** and chelirubine **72** (85CPB4139). The presence of an alkoxy group para to the position to be cyclized in the *aliphatic* formamide



	R^1	R^2	R^3	R^4
29	H	OCH_3	OCH_3	H
47	H	OCH_3	OCH_3	OCH_3
48	OCH_3	OCH_3	OCH_3	OCH_3
49	H	OCH_2O		H

	R^1	R^2	R^3	R^4
50	H	OCH_3	OCH_3	H
51	H	OCH_3	OCH_3	OCH_3
52	OCH_3	OCH_3	OCH_3	OCH_3
53	H	OCH_2O		H

	R^1	R^2	R^3	R^4
54	H	OCH_3	OCH_3	H
55	H	OCH_3	OCH_3	OCH_3
56	OCH_3	OCH_3	OCH_3	OCH_3
57	H	OCH_2O		H

	R^1	R^2	R^3	R^4
58	H	OCH_3	OCH_3	H
59	H	OCH_3	OCH_3	OCH_3
60	OCH_3	OCH_3	OCH_3	OCH_3
61	H	OCH_2O		H

	R^1	R^2	R^3	R^4
4	H	OCH_3	OCH_3	H
10	H	OCH_3	OCH_3	OCH_3
62	OCH_3	OCH_3	OCH_3	OCH_3
7	H	OCH_2O		H

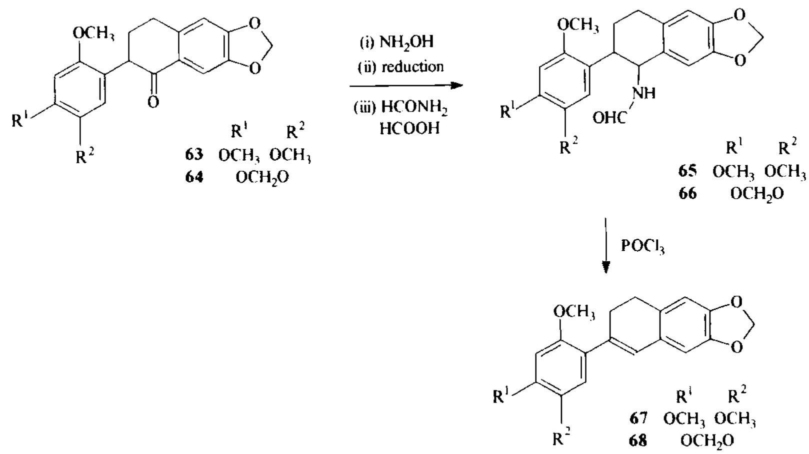
SCHEME 6

(absent in **65** and **66**) is a minimum requirement for success in cyclization to the tetrahydrobenzo[*c*]phenanthridines by means of the Bischler–Napieralski reaction. Otherwise, the β-elimination product formed by the loss of formamide becomes the sole product (**67,68**) instead of the

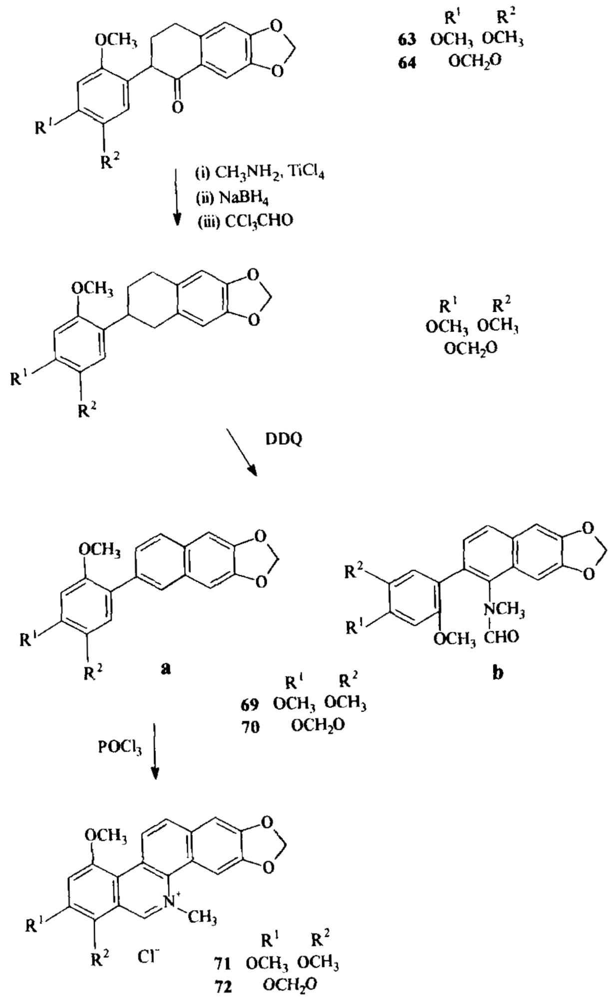
desired cyclized product (Scheme 7). However, when the equivalent *N*-methylnaphthylformamides **69,70** were prepared, Bischler–Napieralski cyclization to the quaternary benzo[*c*]phenanthridines [84J(P1)2283] (**71,72**) proceeded smoothly (Scheme 8). This was attributed to a combination of factors, including the absence of a β-proton on the formamide group, which excluded the possibility of β-elimination to the stilbene, to conjugation between the 2-aryl moiety and the naphthyl ring, ensuring coplanarity and giving two possible conformers (**69a,b** or **70a,b**). Steric repulsion between the ortho function of the aryl group and the formyl in conformers **69b** and **70b** favors conformers **69a** and **70a** and thus promotes Bischler–Napieralski cyclization to the 7,8,10-substituent pattern in the benzo[*c*]phenanthridines. In addition to these two factors, the reactive species from the *N*-methylformamide group of the aromatic naphthylamine intermediate was assumed to be more reactive than the aliphatic NH-formamide, and therefore promoted cyclization in the absence of a para alkoxy group ($^{+}N(Me){=}CHOPOCl_2$ versus $N{=}CHOPOCl_2$).

Anomalies in the Bischler–Napieralski reaction were later reported (95TL2795) when substituents in the 2-aryl group of the aromatic *N*-methylnaphthylformamide were of a 2-alkoxy-4,5-methylenedioxy nature (**70**), but not with the equivalent 2-alkoxy-4,5-dimethoxy pattern (**69**). The former cyclized to a 12-azonianaphth[1.2-*b*]azulene derivative **73** as an additional product to **72,** whereas the latter cyclized normally to the benzo-[*c*]phenanthridinium chloride **71** (Scheme 9).

Ishii's synthetic sequence could not initially be applied to the synthesis of phenolic benzo[*c*]phenanthridines such as fagaronine (**3**), because the steps involving the hydrogenolysis of the γ-oxobutyric acids to the butyric

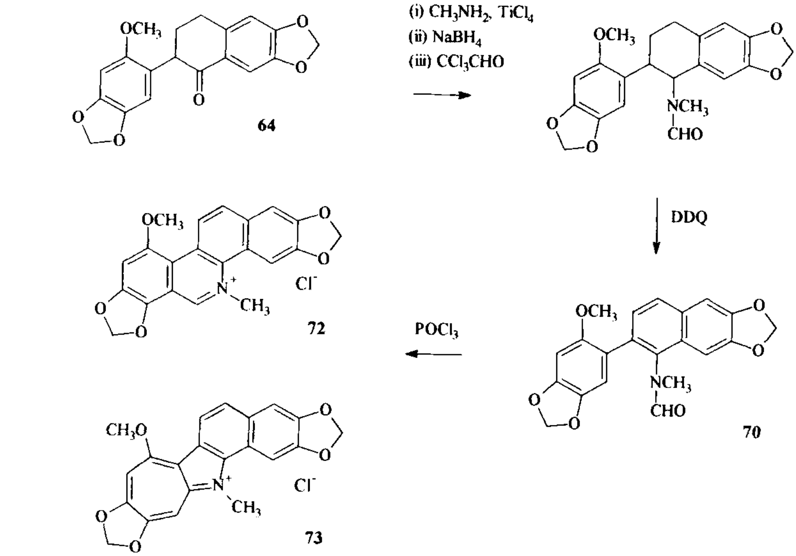


SCHEME 7

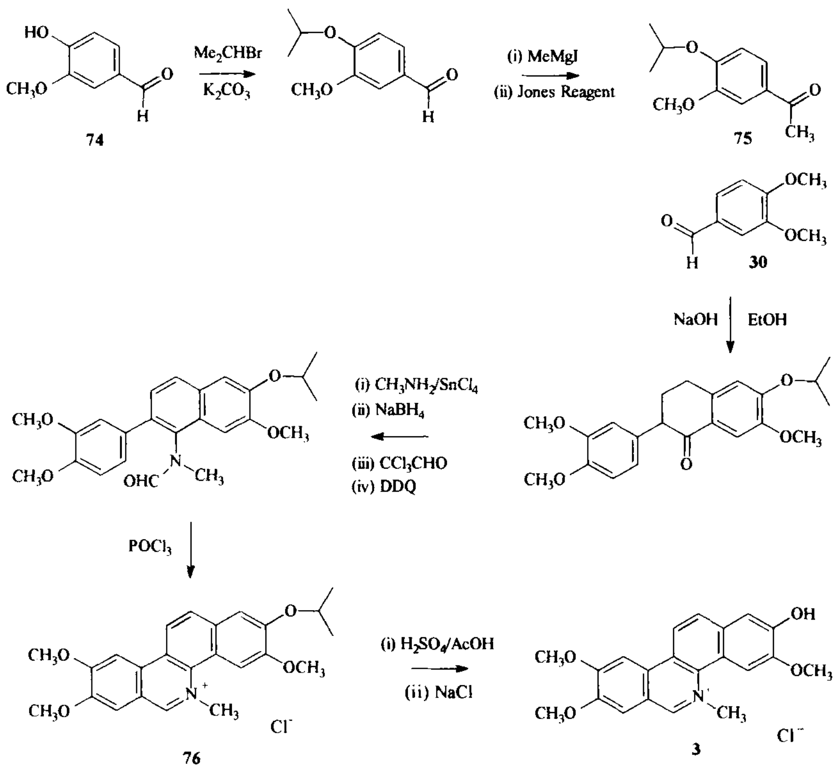


SCHEME 8

acids and their subsequent intramolecular acylation with phosphorus oxychloride to the 2-aryl-1-tetralones involved procedures that caused cleavage of common phenolic protecting groups such as benzyl or methoxymethyl substituents (85CPB4139; 87CPB2717). However, an isopropoxy protecting group proved less susceptible to cleavage, enabling fagaronine to be synthesized successfully using this method [87JCS(P1)671] (Scheme 10). Reaction of isovanillin **74** with isopropyl bromide in the presence of potassium carbonate, followed by Grignard reaction with methylmagnesium iodide and oxidation of the secondary alcohol with Jones reagent, yielded the acetophe-



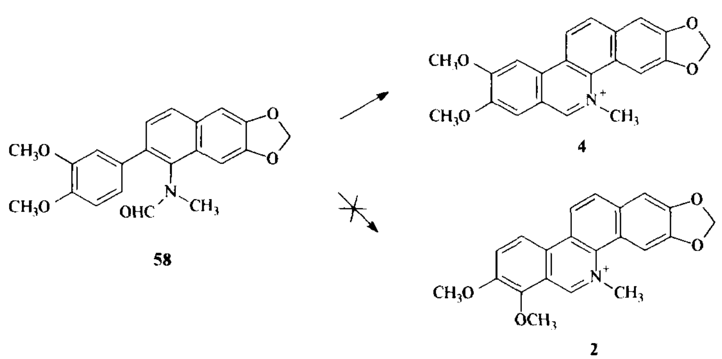
SCHEME 9



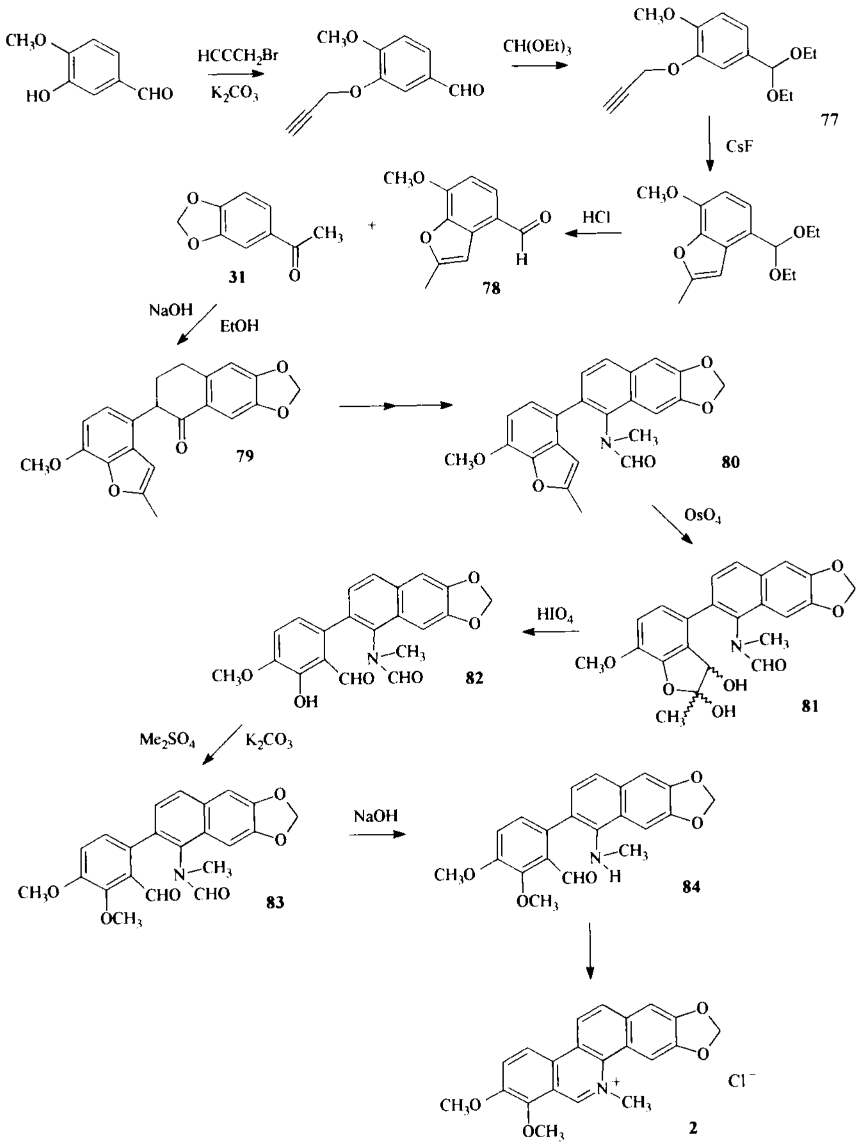
SCHEME 10

none precursor **75** to be condensed with veratraldehyde **30.** Their standard procedure (85CPB4139) led to *O*-isopropylfagaronine **76,** with cleavage to fagaronine **3** accomplished using concentrated sulfuric acid in acetic acid or boron trichloride in dichloromethane, the former reagents producing a better yield (15.7% overall) (Scheme 10) [87JCS(P1)671].

Ishii's synthetic route also originally lacked applicability to the synthesis of the 7,8-dioxygenated benzo[*c*]phenanthridines such as chelerythrine (**2**) because the Bischler–Napieralski reaction of the aromatic *N*-methylnaphthylformamide produced exclusively 8,9-substituted benzo[*c*]-phenanthridines through cyclization of the formyl group para rather than ortho with respect to the C_3-methoxy group of the 2-aryl moiety (Scheme 11) [83CPB3024, 83CPB3039; 84J(P1)2283; 85CPB4139; 87CPB2717, 87JCS(P1)671; 95TL2795]. A method was therefore required that avoided the Bischler–Napieralski cyclization to form ring C. This was achieved by forming the propargyl ether of the diethylacetal of isovanillin (**77**) followed by CsF-mediated Claisen rearrangement and subsequent acetal hydrolysis to give the 4-formyl-7-methoxy-2-methylbenzo[*b*]furan (92CPB1148) (**78**) (Scheme 12). Following the established procedure with acetopiperone (**31**) in the initial Claisen–Schmidt aldol condensation, the aromatic *N*-methyl-naphthylformamide **80** was produced via the 2-aryl-1-tetralone intermediate **79** as before (83CPB3024, 83CPB3039). Treatment of the furan moiety of the 2-aryl-*N*-methyl naphthylformamide **80** with osmium tetroxide yielded the diol **81,** which underwent cleavage to the salicylaldehyde **82** with periodic acid with subsequent conversion to the methyl ether **83** by methylation with dimethyl sulfate. In order to form ring C, it was necessary to hydrolyze the *N*-formyl group to the naphthyl-*N*-methylamine **84,** which then spontaneously condensed with the aldehyde moiety to form chelerythrine (**2**) (92CPB2002) in an overall yield of 6.8%.



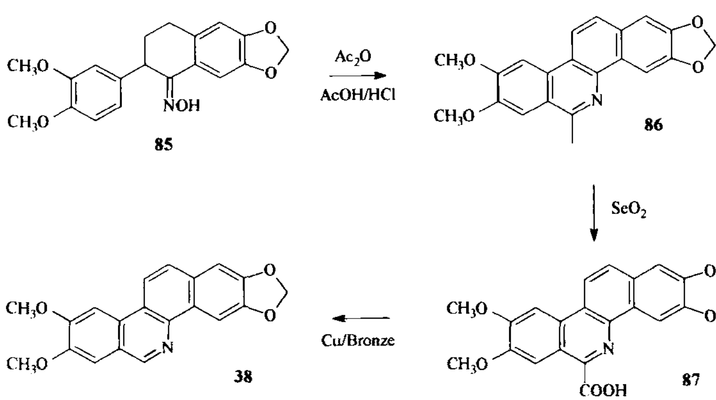
SCHEME 11



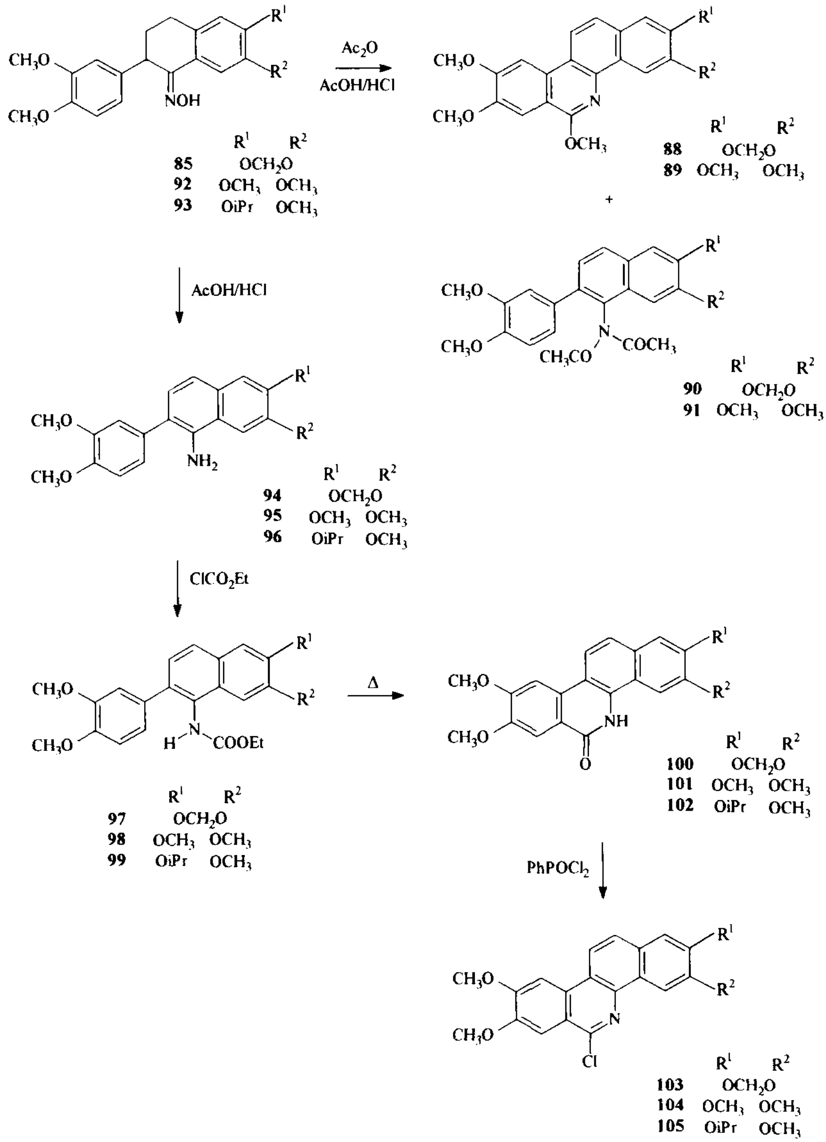
SCHEME 12

A more recent synthesis via the 2-aryl-1-tetralone intermediate developed by Janin and Bisagni (93T10305) provides a route to the benzo[c]phenanthrid-6(5*H*)-ones and 6-chlorobenzo[c]phenanthridines. Synthesis of

the tetralone was achieved using the standard procedures developed by Ishii, from where the formation of ring C involved the thermal cyclization of a urethane. Such an approach necessitated the initial preparation of an aromatic 2-aryl-1-naphthylamine. Under classical Semmler–Wolff reaction conditions, treatment of the 2-aryl-1-tetralonoxime **85** with a hydrogen-chloride-saturated mixture of acetic acid and acetic anhydride yielded the cyclized nor-6-methylbenzo[*c*]phenanthridine **86,** as reported by Zee-Cheng and Cheng (75JMC66) (Scheme 13). Gopinath *et al.* (59JCS4012) have also reported using this method to synthesize the 6-methyl analogue **86,** which they oxidized with excess selenium dioxide to the 6-carboxylic acid **87,** which underwent decarboxylation by heating with copper bronze to nor-nitidine (**38**) (Scheme 13). Janin and Bisagni (93S57, 93T10305) reported the presence of additional reaction products when the Semmler–Wolff method was used with the oximes **85,92,** such as the 6-methoxybenzo[*c*]phenanthridines **88,89** and the *N,N*-diacetylated-2-arylnaphthylamine derivatives **90,91** in variable amounts (which proved to be stable to complete hydrolysis, yielding only the monoacetylated compounds and not the primary amine). However, removal of acetic anhydride from the Semmler–Wolff reaction conditions produced the desired 2-aryl-1-naphthylamines **94–96** from the 2-aryl-1-tetralonoximes **85,92,93.** To obtain the benzo[*c*]phenanthrid-6(5*H*)-ones **100–102** from these amines, urethanes **97–99** were prepared by treatment with ethyl chloroformate and thermally cyclized (70JHC1191), probably via a pericyclic mechanism. Chlorination of the benzo[*c*]phenanthrid-6(5*H*)-ones to give the 6-chlorobenzo[*c*]phenanthridine analogues **103–109** was achieved with phenylphosphonic dichloride (Scheme 14). Reaction with dimethylaminoethylamine gave the 6-(dimethylaminoethyl)benzo[*c*]phenanthridines (**17,18**).



SCHEME 13



SCHEME 14

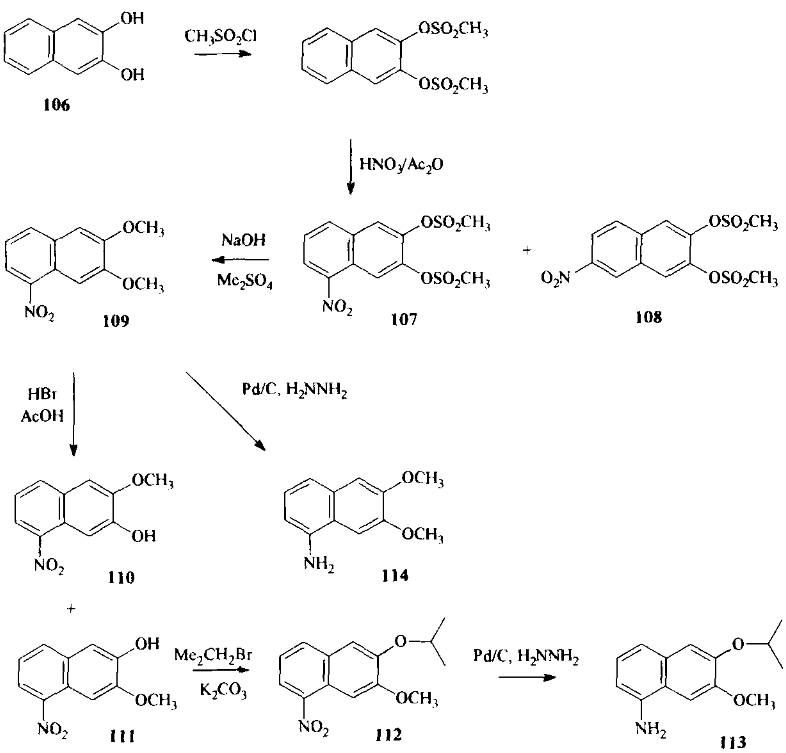
2. *Synthesis via Naphthalene Intermediates*

Alternative routes have been developed that rely on the construction of ring C as the last step in forming the benzo[c]phenanthridine nucleus, but

do not involve the 2-aryl-1-tetralone intermediate. Rings A and B are generally provided by a tetralone or naphthylamine precursor, whereas construction of rings D and C has been approached in a variety of ways.

Stermitz and co-workers' (74JOC3239) synthetic pathway to fagaronine (**3**) and *O*-methylfagaronine (**5**) involving the initial preparation of the appropriately substituted naphthylamine intermediate proved problematic at the first step. Nitration of 2,3-dimethoxynaphthalene with nitric acid in acetic acid gave all three possible nitro isomers. Successive fractional crystallization isolated the required 5-nitro isomer only as the minor product. This was improved (75JMC708) by utilizing the strong electron-withdrawing effect of mesyl substituents in place of the methyl groups by reaction of 2,3-dihydroxynaphthalene **106** with methanesulfonyl chloride, followed by nitration to produce the required 5-nitro isomer **107** as the major product, which precipitated out uncontaminated by the corresponding 6-nitro isomer **108.** The dimesyloxy to dimethoxy transformation was brought about by successive treatment with sodium hydroxide solution and dimethyl sulfate, producing the desired 5-nitro-2,3-dimethoxynaphthalene **109** in 40% yield from the 2,3-dihydroxynaphthalene. For the synthesis of fagaronine, cleavage of the 2,3-dimethoxy-5-nitronaphthalene using HBr and acetic acid yielded a 1 : 1 mixture of the monomethoxy isomers **110,111,** which were readily separated by crystallization. The required 3-hydroxy-2-methoxy isomer **111** was isopropylated **112** and the nitro group reduced with Pd/C and hydrazine to the naphthylamine intermediate **113.** The 2,3-dimethoxynaphthylamine **114** was obtained by direct reduction of the 5-nitro isomer **109** (Scheme 15).

For rings C and D, the authors referred to the work of Kessar *et al.* [72J(P1)1158, 72T167, 72T177], who, in developing new routes to phenanthridines, had established that haloanils and their hydrogenated amine analogues could be cyclized in 90% yield by treatment with excess amide ions in liquid ammonia via a benzyne intermediate. For cyclization to take place, strong anionic activation of the aromatic ring was a prerequisite, as aryl groups normally do not attack benzynes unless a negatively charged oxygen confers nucleophilicity on the ortho and para positions in the aryl ring. Kessar *et al.* demonstrated that treatment of the reduced enamine (**115,** Fig. 4) formed between aniline and *o*-chlorobenzaldehyde with potassium amide in liquid ammonia conferred nucleophilicity on the aryl ring and thus enabled intramolecular attack of the benzyne moiety to yield the 5,6-dihydrophenanthridine. Treatment of the haloanil (**116,** Fig. 4) under the same conditions affords the fully aromatic phenanthridine system, probably via prior addition of the amide ion across the azomethine linkage. In the absence of strong anionic activation, intramolecular attack does not proceed to any significant extent, as is evident by the nonreactivity of the *N*-



SCHEME 15

methylamine (**117**, Fig. 4) and amide analogues (**118**, Fig. 4). The former will not react because an exchangeable proton is absent under strongly basic conditions.

Cyclization of the anils having alkyl or alkoxy groups in the benzyne moiety was found to proceed smoothly, but in certain disubstituted cases, such as 4,5-dimethoxy or 4,5-methylenedioxy in the benzyl moiety, the yields were modest [72JCS(P1)1158; 74IJC323]. Stermitz and co-workers

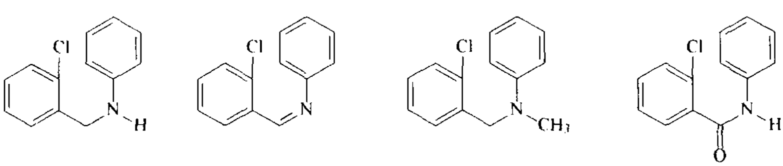
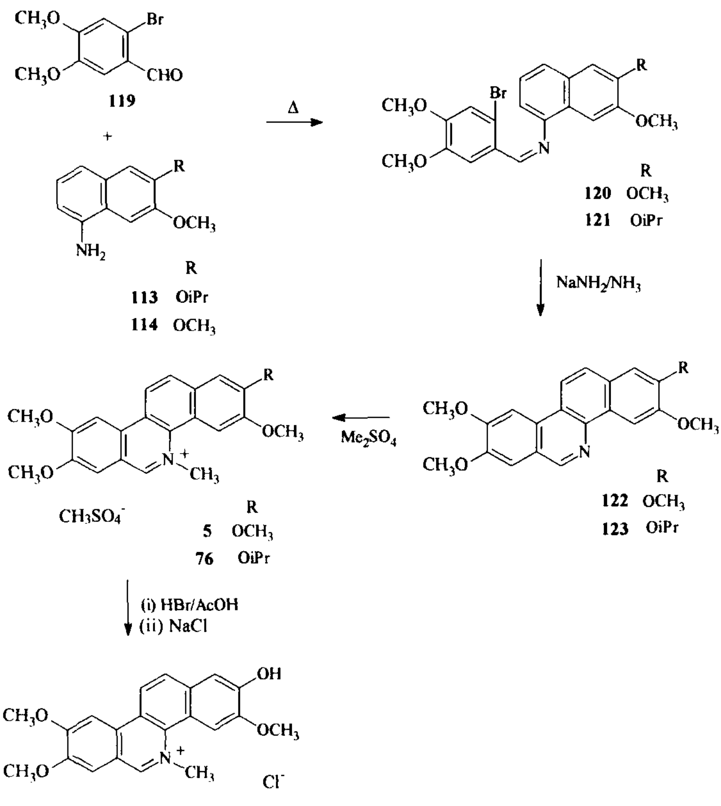


FIG. 4

(74JOC3239; 75JMC708) applied this method to the synthesis of the benzo[*c*]phenanthridine nucleus by reacting the naphthylamine intermediates **113,114** with *o*-bromoveratraldehyde **119** to produce the bromoanils **120,121,** which cyclized under the conditions described to the benzo[*c*]phenanthridines **122,123** (Scheme 16). Methylation to the quaternary benzo[*c*]-phenanthridines **5** and **76** and cleavage of the isopropyl group was achieved using dimethyl sulfate and HBr in acetic acid, respectively, producing fagaronine **3** in an overall 5.2% yield. Where protecting groups were not necessary, as in the case of *O*-methylfagaronine (**5**), the yield was improved to 10–12%.

The cyclization of the bromoanil is not a major shortcoming of this route to the 7,8-substituted target compounds such as chelerythrine **63** where yields are higher (63%) (88JOC1708). The reason for the reduction in yields



SCHEME 16

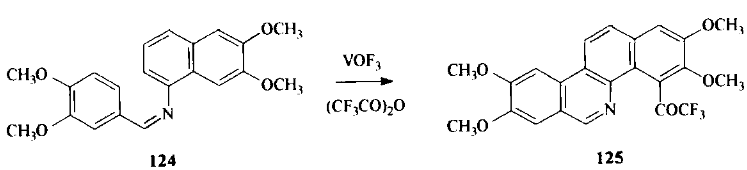
associated with the 8,9-substituent pattern was attributed to the absence of an ortho substituent to force the arylamino sidechain proximal to the benzyne moiety to promote intramolecular cyclization, thus allowing competitive nucleophilic attack by the amide ion at the benzyne group.

Kessar *et al.* (88JOC1708) demonstrated that lowering the reaction temperature and increasing the size of the competing external nucleophile by substituting lithium diisopropylamide (LDA) for potassium amide dramatically improved cyclization, giving comparable yields with the 7,8-substituted compounds.

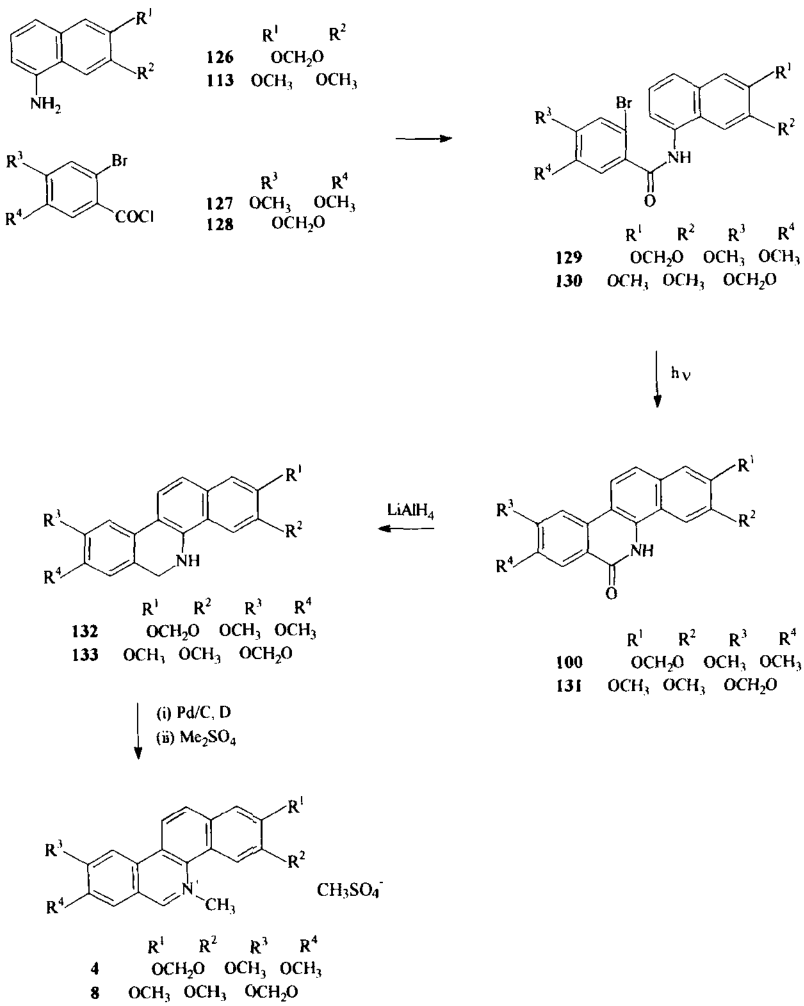
Stermitz and co-workers (79JOC293), in attempting to overcome the reduced yields associated with the 8,9-substituted compounds, failed to synthesize *O*-methylfagaronine (**5**) when using electrochemical techniques to cyclize the bromoamine, yet achieved a 50% yield of the 4-trifluoroacetyl analogue **125** when the naphthylimine **124** was oxidized with VOF_3 in trifluoroacetic anhydride (Scheme 17).

Using the benzyne-mediated intramolecular cyclization mechanism, it was not possible to form ring C if rings D and A/B were linked through an amide because of insufficient nucleophilic activation of the aromatic system. However, two independent groups were able to use photochemical methods to promote cyclization in *ortho*-bromo-substituted amides.

Kessar *et al.* (74TL2269) reacted the appropriately substituted naphthylamine (**113,126**) with 2-bromo-4,5-dimethoxybenzoyl chloride **127** or 2-bromo-4,5-methylenedioxybenzoyl chloride **128** to form the corresponding amides **129,130,** which underwent photocyclization to the tetracyclic amides (**100,131**) in 48–70% yields (Scheme 18). Reduction with lithium aluminum hydride followed by dehydrogenation and methylation yielded the quaternary benzo[*c*]phenanthridines nitidine **4** and allonitidine **8.** The pentaalkoxy benzo[*c*]phenanthridine alkaloids chelilutine **71** and sanguilutine **141** were not accessible via benzyne-mediated cyclization of the haloanils (an alkoxy substituent ortho to the halogen negates benzyne formation). However, by use of the photochemical method (77TL1459), they were readily obtainable from the reduced haloanils, prepared by condensation of the appropriate naphthylamine (**114,126**) with 2-bromo-3,5,6-trimethoxybenzaldehyde **134** to give the bromoanils **135,136,** followed by reduction to the amines **137,138.**



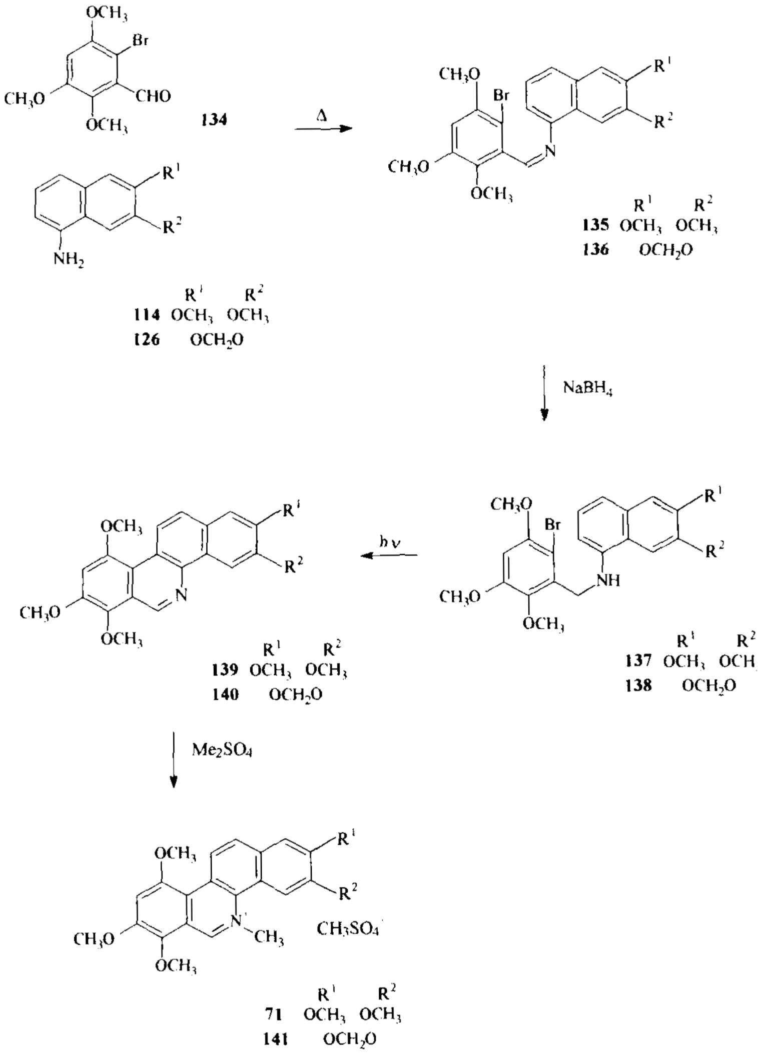
SCHEME 17



SCHEME 18

Irradiation afforded norchelilutine **139** and norsanguilutine **140** in 50% yields (Scheme 19).

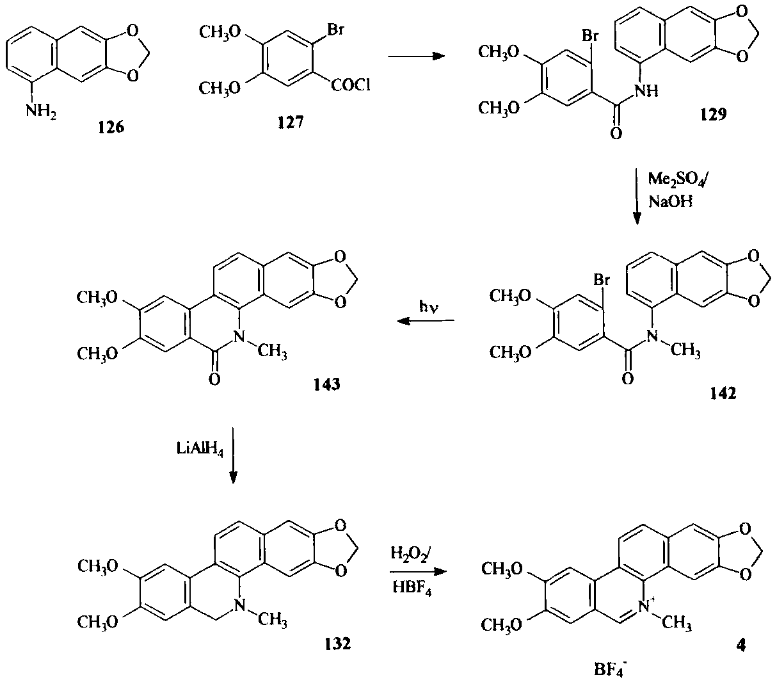
In a separate development, Begley and Grimshaw [77JCS(P1)2324] attempted to cyclize the tertiary amide **142** by both photochemical and electrochemical methods. Reaction of 6,7-methylenedioxynaphthylamine **126** with 2-bromo-4,5-dimethoxybenzoylchloride **127** afforded the benzamide **129,** which was methylated to give the tertiary amide **142.** Whereas electrochemical reaction was unsuccessful, photochemical cyclization to the *N*-



SCHEME 19

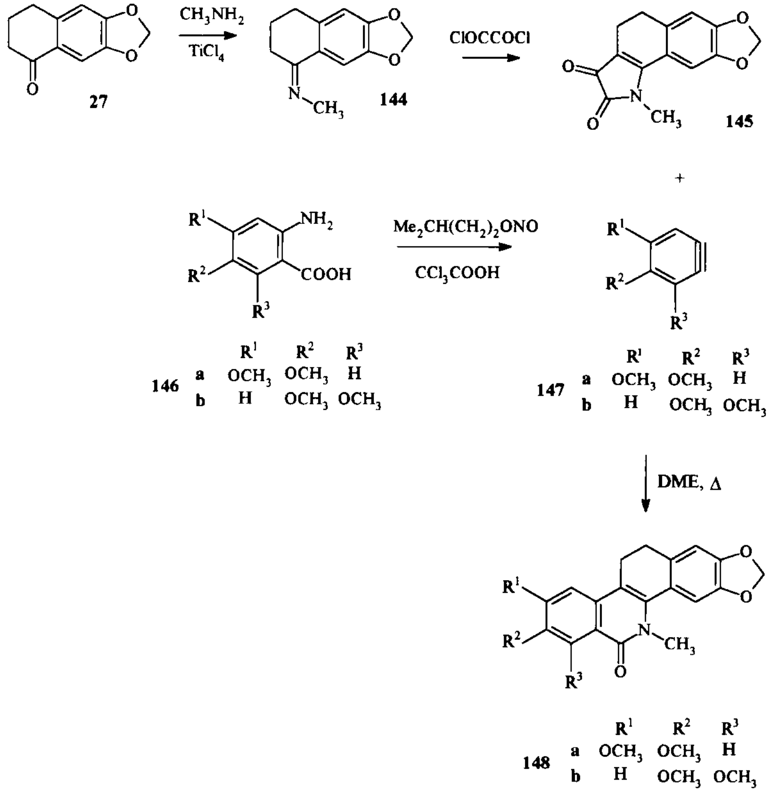
methylbenzo[c]phenanthridin-6-one, oxynitidine **143,** occurred in 35% yield. Reduction with lithium aluminum hydride to dihydronitidine **132** followed by oxidation with hydrogen peroxide in acidic solution yielded nitidine **4** (Scheme 20).

Castedo and co-workers (87TL2407; 92JOC5907) have developed a highly convergent strategy to the benzo[c]phenanthridines based on the ability of dihydronaphthalenopyrrolinediones to undergo (4+2) cycloaddi-



SCHEME 20

tions with the highly electrophilic benzyne system (intramolecular benzyne cycloaddition). The tendency of the primary cycloadduct to lose carbon monoxide (86JOC2718) makes the construction of tetracyclic dihydrobenzo[*c*]phenanthridin-6(5*H*)-ones easily achievable via this route. This strategy proved valid for both 2,3,8,9- and 2,3,7,8-oxygenated dihydrobenzo[*c*]-phenanthridin-6(5*H*)-ones. The methylenedioxytetralone **27** was converted to the methylimine **144** and then treated with oxalyl chloride under carefully controlled conditions to provide the desired dihydronaphthalenopyrrolinedione **145** (Scheme 21). Reaction with benzyne **147** (carried out by adding a slurry of benzenediazonium carboxylate **146** to a refluxing solution of the dihydronaphthalenopyrrolinedione **145** in ethylene glycol dimethyl ether), initially through nucleophilic attack via the enamine on the electrophilic benzyne, followed by carbon monoxide extrusion, produced the dihydrobenzo[*c*]phenanthridin-6(5*H*)-one precursor of nitidine **148a** in 29% yield (with respect to the cycloaddition reaction). The synthesis of the chelerythrine analogue involved the reaction of the unsymmetrically substituted 3,4-dimethoxybenzyne **147b** with the dihydronaphthalenopyrrolinedi-



SCHEME 21

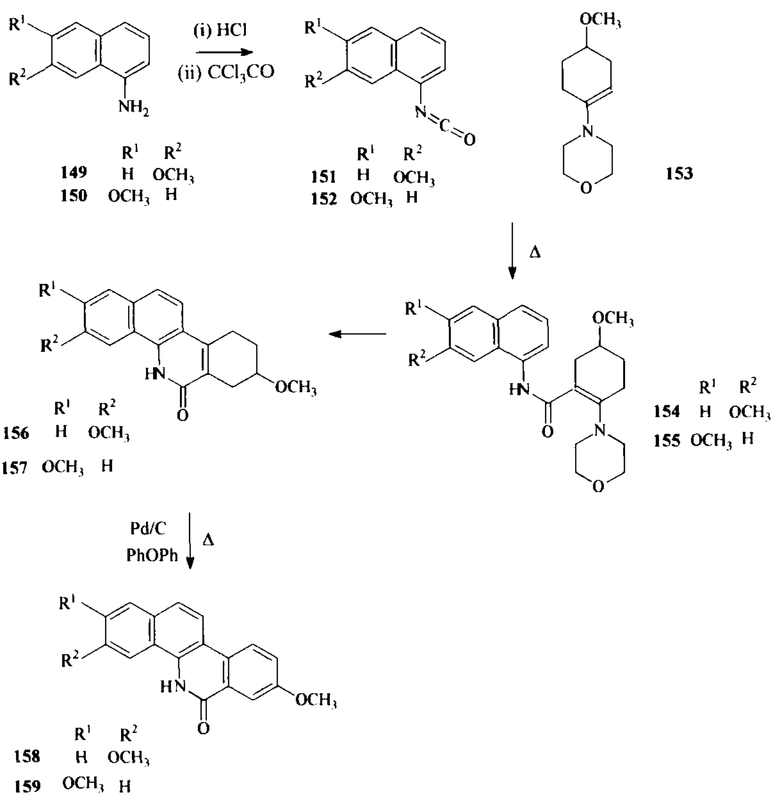
one **145.** The detection of only the required 2,3,8,9-substituted isomer **148b** in 29% yield confirmed the regioselectivity of this method.

Bisagni and co-workers (93JMC3686) have prepared 2,8- and 3,8-dioxygenated benzo[c]phenanthridin-6(5*H*)-ones where the key step is based on the preparation of 7,8,9,10-tetrahydrobenzo[c]phenanthridin-6(5*H*)-ones from 1-naphthyl isocyanates and cyclohexanone enamines (77IJC960). From the hydrochloride salts of 1-naphthylamines **149,150,** prepared by the modified Semmler–Wolff conditions described in their earlier papers (93S57, 93T10305), the corresponding isocyanates **151,152** were formed using triphosgene. Direct treatment of the hot isocyanate solution with the monomethoxy enamine **153** gave the intermediate amides **154,155,** which upon continued heating of the hydrogen-chloride-saturated medium underwent cyclization to the 7,8,9,10-tetrahydrobenzo[c]phenanthridin-6(5*H*)-ones **156,157** in 20–50% yields. Dehydrogenation of ring D

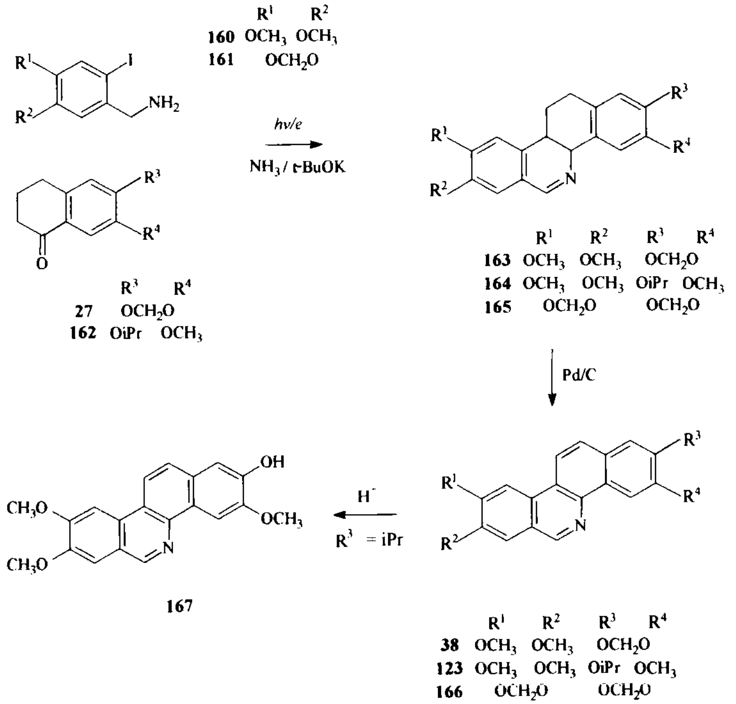
with 10% Pd/C yielded the benzo[c]phenanthridin-6(5H)-ones **158,159** (Scheme 22).

Beugelmans, having developed the extended $S_{RN}1$ reaction (84BSB547) to the synthesis of isoquinolinones (81S729) and isoquinolines (82TL2313) from 2-halobenzamides or 2-halobenzylamines and nucleophiles derived from ketones, applied the method to the synthesis of benzo[c]phenanthridines (85JOC4933). The rationale was to react the appropriately substituted iodobenzylamines **160,161** with substituted tetralones **27,162** as the nucleophilic enolates under $S_{RN}1$ conditions to yield the 2-aryltetralones. The amine functionality ortho in the aryl moiety to the newly formed ring D/B link would then condense with the keto group to yield the tetracyclic nucleus (Scheme 23).

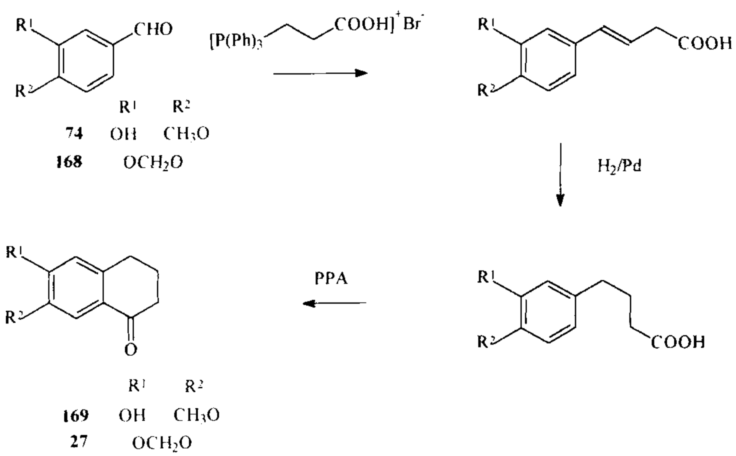
Synthesis of the substituted tetralones (Scheme 24) relied on the Wittig reaction between the bromoproprionic acid phosphonium salt with isovanil-



SCHEME 22



SCHEME 23



SCHEME 24

lin **74** or piperonylaldehyde **168.** Subsequent reduction of the alkenes with H_2/Pd followed by cyclization with PPA gave the desired tetralones **27,169.** The tetralone precursor for norfagaronine was prepared by protecting the phenolic functionality with an isopropyl group **162.**

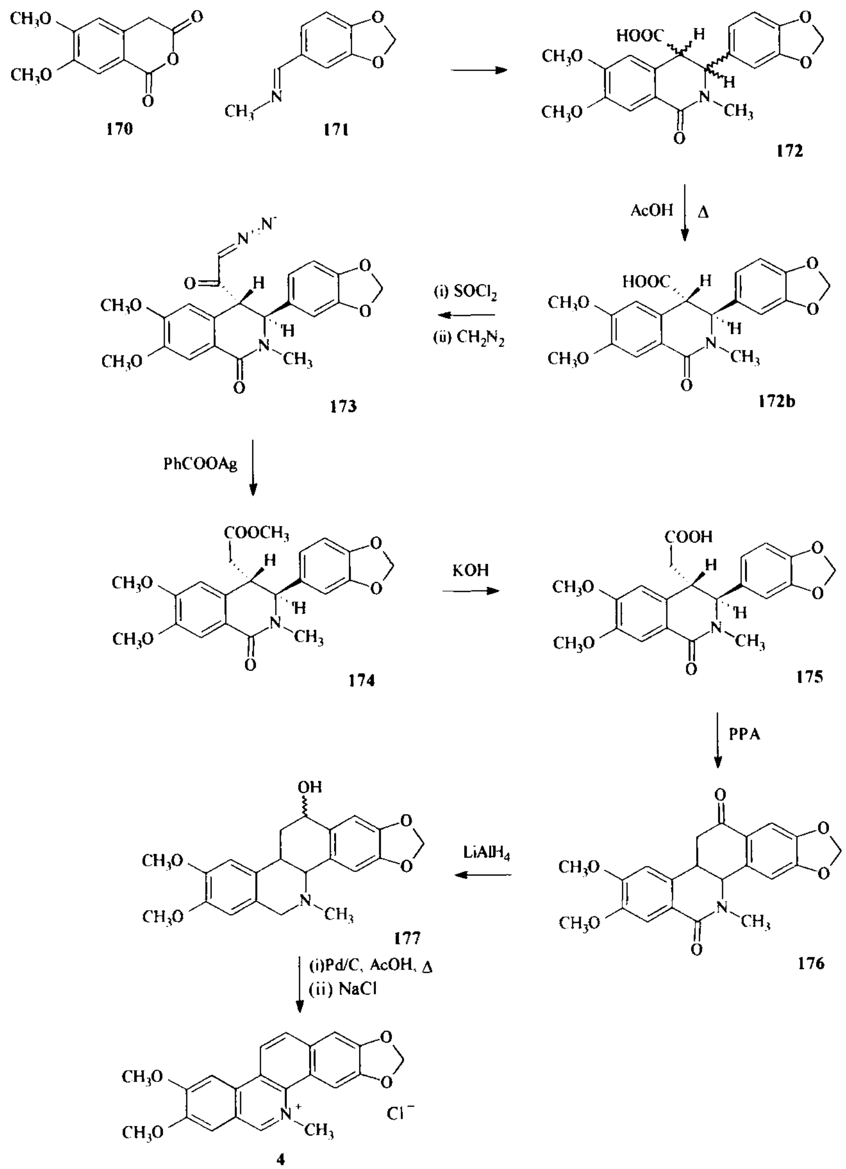
Reaction of the tetralones **27,162** with the substituted iodobenzylamines in the presence of potassium *tert*-butoxide in liquid ammonia and UV illumination gave the tetracyclic ring systems **163–165** directly. Oxidation to the norbenzo[*c*]phenanthridines **38,123,166** was achieved by direct heating with Pd/C without solvent. Removal of the isopropyl group was under acidic conditions. The overall yields calculated upon the starting materials used for preparing the substrates and nucleophiles were 25% for nornitidine **38,** 16% for norfagaronine **167,** and 7% for noravicine **166.**

B. Final Cyclization of Ring B

1. *Synthesis via the 3-Arylisoquinoline Intermediate*

The first benzo[*c*]phenanthridine synthesis via the final ring closure of ring B was developed by Cushman (78JOC286) in order to produce nitidine **4.** The basis of this approach was to produce the 3-arylisoquinolin-1-one **175,** thus providing ring A, C, and D of the tetracyclic benzo[*c*]phenanthridine with a two-carbon functionality with which to form ring B. The rapid exothermic reaction between 4,5-dimethoxyhomophthalic anhydride **170** and the enamine 3,4-methylenedioxybenzylidinemethylamine (77JOC1111) (**171**) afforded a diastereomeric mixture of *cis*- and *trans*-*N*-methyl-3-aryl-4-carboxymethylisoquinol-1-ones (**172a,b**). With heating in acetic acid, the cis diastereoisomer epimerized to the thermodynamically more stable trans isomer (**172b**), which meant in practice that the trans isomer could be obtained *in situ* in 92% yield without the need to separate the two diastereoisomers. Treatment of the acid chloride of the *trans*-*N*-methyl-3-aryl-4-carboxymethylisoquinol-1-one with diazomethane gave the diazoketone **173,** which with the use of silver benzoate underwent Wolff rearrangement to the methyl ester **174.** Hydrolysis of the methyl ester to the acid **175,** followed by intramolecular Friedel–Crafts acylation with polyphosphoric acid, yielded the tetracyclic ketone **176.** Reduction with lithium aluminum hydride followed by dehydration and dehydrogenation of the resulting diastereomeric mixture of the amino alcohol **177** with Pd/C in acetic acid gave nitidine **4** in an overall 9% yield (Scheme 25).

Waigh and co-workers [81MI3; 90JCS(P1)2657] developed a route based on a two-stage synthesis of the 3-arylisoquinolone intermediates, which provides all but two carbons of the tetracyclic ring system and a suitable functionalization for the remaining ring B to be formed. The aminonitriles



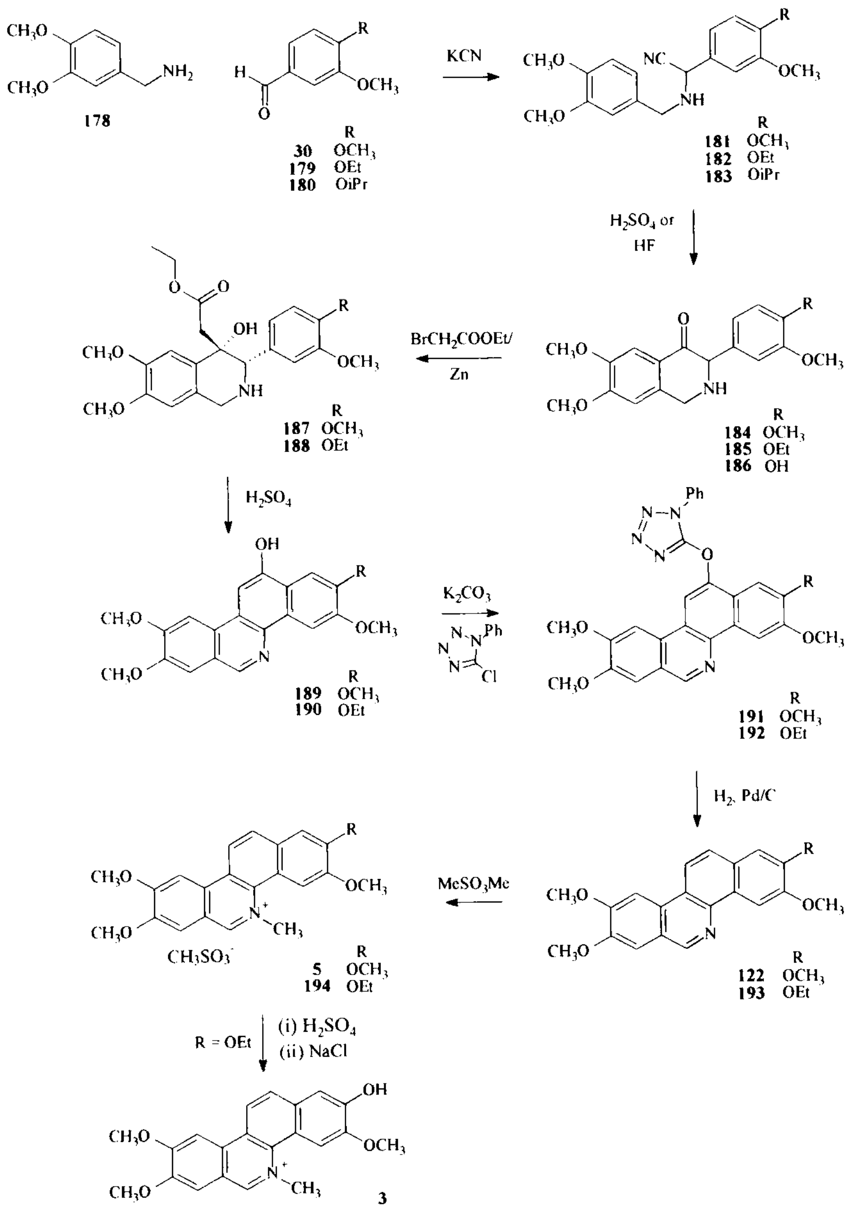
SCHEME 25

181–183 were produced by the reaction between veratrylamine **178** and an appropriately substituted benzaldehyde **30,179,180** for ring A under Strecker conditions. The tetramethoxyisoquinolin-4-one **184** was formed

by sulfuric acid cyclization of the aminonitrile **181** in 54% yield (Scheme 26). To prepare fagaronine, the ethyl-protected aminonitrile **182** was used, which gave a 29% yield of the 3-arylisoquinolin-4-one **185** in sulfuric acid. The yield was improved to 68% by using anhydrous hydrofluoric acid as the cyclizing agent. The yield of the tetramethoxyisoquinolin-4-one **184** was also improved (66%) when HF was used in place of sulfuric acid; however, both reagents produced the phenolic isoquinolinone **186** when the isopropyl-protected aminonitrile **183** was cyclized. The next step demanded a two-carbon synthon with appropriate substitution for generation of a nucleophile and with functionality on the second carbon suitable for acid-catalyzed ring closure of ring B. Reaction of ethyl bromoacetate under Reformatski conditions yielded the β-hydroxyesters **187,188** in excess of 80%, which were cyclized in sulfuric acid to give the fully aromatic 12-hydroxybenzo[*c*]phenanthridines **189,190** in 52 and 70% yields, respectively. Formation of the tetrazolyl ethers **191,192** followed by hydrogenation under pressure with palladium on charcoal gave the dehydroxylated benzo[*c*]phenanthridines **122,193.** Quaternization with methyl methanesulfonate proceeded almost quantitatively (**5,194**), with the ethyl group being cleaved by concentrated sulfuric acid (94BSF718) to yield fagaronine (**3**) in an overall yield of 18%.

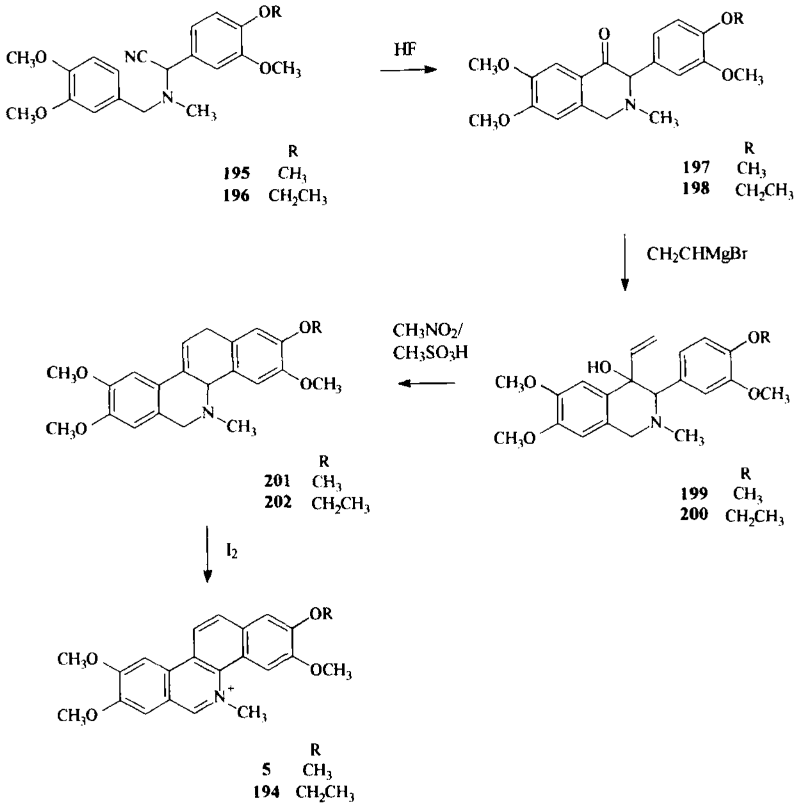
Duval and co-workers have modified this route (95TL5731) in order to reduce the number of steps required to reach the benzo[*c*]phenanthridines. Grignard addition of vinylmagnesium bromide to provide the two-carbon synthon to the tertiary *N*-methylisoquinolin-4-ones **197,198** (prepared via the cyclization of the tertiary *N*-methylaminonitriles **195,196** in anhydrous hydrofluoric acid) furnished the vinyl alcohols **199,200** (Scheme 27), whereas use of the secondary isoquinolin-4-ones **184,185** yielded no vinyl alcohols. Cyclization of the vinyl alcohols was achieved in the presence of the Lewis acid tin(IV) chloride at low temperatures, producing the trihydrobenzo[*c*]phenanthridines **201,202,** but in low yield (49%). However, a nitromethane solution of the vinyl alcohols in the presence of methanesulfonic acid yielded the desired products **201,202** almost quantitatively (94–96%). Incorporation of the *N*-methyl substituent at the commencement of the synthetic procedure enabled the production of the quaternary benzo[*c*]-phenanthridines by direct oxidation with iodine in refluxing ethanol. The overall yields for *O*-methylfagaronine **5** and *O*-ethylfagaronine **194** were 58 and 52%, respectively, representing one of the most effective synthetic routes to the quaternary 2,3,8,9-benzo[*c*]phenanthridines.

The mechanism of cyclization of the aminonitrile to the 3-arylisoquinolin-4-one involves a spiro rearrangement with both anhydrous HF and sulfuric acid [87JCR(S)36] whereby an ortho or para oxygenated substituent is involved in the initial cyclization step with subsequent bond breakage to



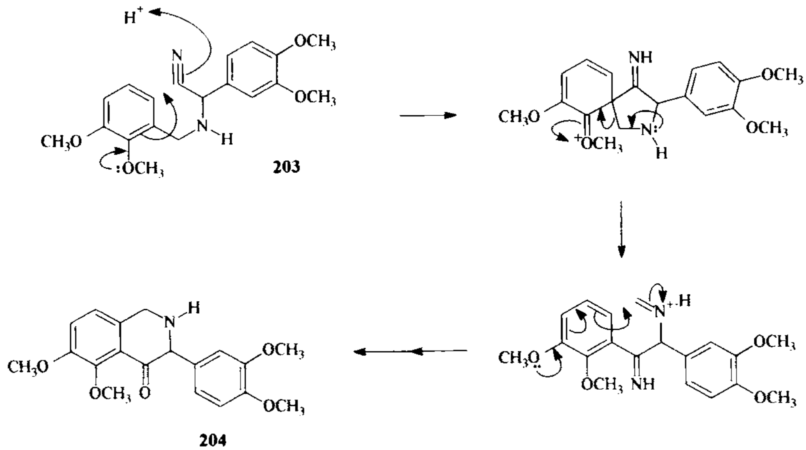
CH3O
CH3O
NH2
178
H
O
R
OCH3
R
30 OCH3
179 OEt
180 OiPr
KCN
NC
NH
R
181 OCH3
182 OEt
183 OiPr
H2SO4 or
HF
O
NH
R
184 OCH3
185 OEt
186 OH
BrCH2COOEt/
Zn
OH
R
187 OCH3
188 OEt
H2SO4
OH
N
R
189 OCH3
190 OEt
K2CO3
N
Ph
Cl
R
191 OCH3
192 OEt
H2, Pd/C
R
122 OCH3
193 OEt
MeSO3Me
CH3
CH3SO3-
R
5 OCH3
194 OEt
R = OEt
(i) H2SO4
(ii) NaCl
3

SCHEME 26

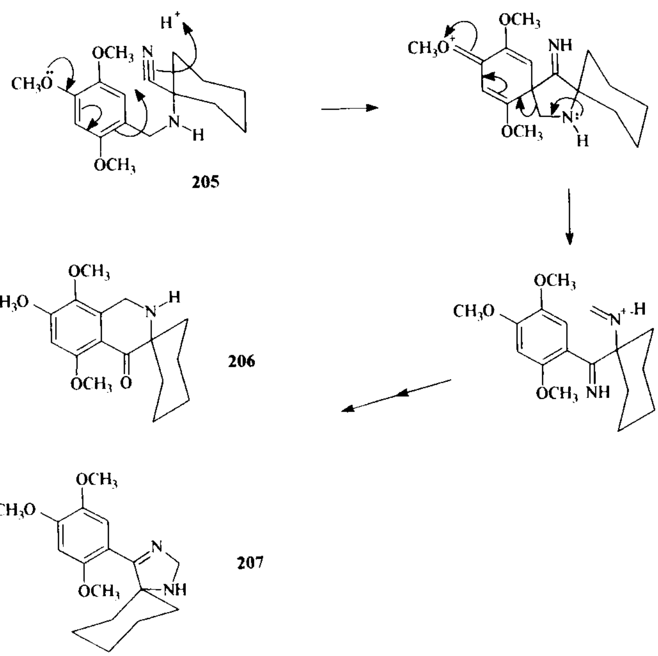


SCHEME 27

generate an intermediate with a reactive iminium moiety and ring formation by conjugation of the meta alkoxy group (Scheme 28). Consequently, this route has so far proved unsuitable for the synthesis of 2,3,7,8-oxygenated benzo[*c*]phenanthridines because of the reversal of the substituent pattern from the aminonitrile **203** to the cyclized 3-aryl isoquinolin-4-one **204** (Scheme 28). The spiro mechanism was also confirmed by cyclization of the trimethoxy aminonitrile **205** to give the isoquinolin-4-one **206** and the imidazoline [91JCR(S)58] **207,** the latter forming by intramolecular attack via the imine nitrogen at the iminium carbon to form the imidazoline as opposed to the meta methoxy group conjugating through the ring to form the isoquinolin-4-one (Scheme 29). Gavin and Waigh attempted to prepare the 7,8-oxygenated isoquinolines using methylthio substituents to direct cyclization of the aminonitriles with subsequent removal of the directing group by hydrogenation. Their success was limited to the formation of 3-



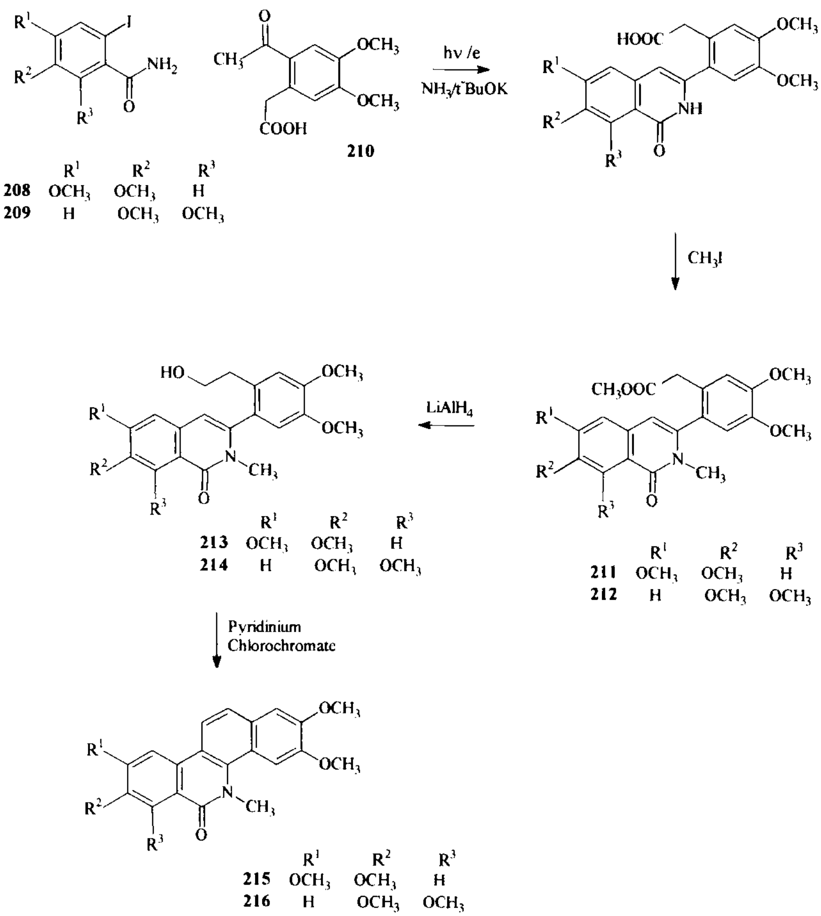
SCHEME 28



SCHEME 29

cyclohexylisoquinolin-4-ones; the 3-arylisoquinolin-4-ones tended to oxidize too readily [90JCS(P1)503].

Bengelmans and Bois-Choussy (92T8285) have also used the radical nucleophilic substitution reaction ($S_{RN}1$) of *ortho*-functionalized aryl halides with ketone-derived enolates as the nucleophiles as a means toward final closure of ring B in benzo[*c*]phenanthridine synthesis. The strategy behind this method is that the nucleophilic enolate, having been regiospecifically introduced at the site of the leaving group (the halide), can react in further steps via its ketone group, with the ortho functionality of the substrate to produce the 3-arylisoquinoline intermediates (Scheme 30). This

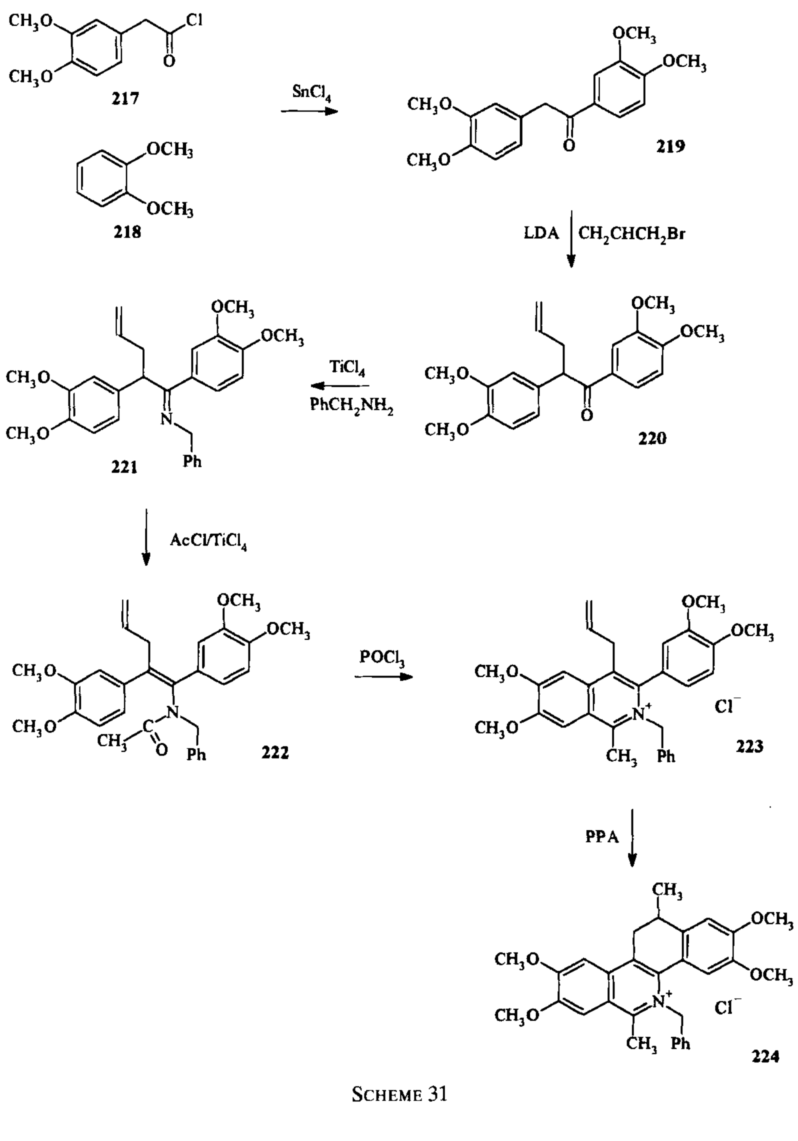


SCHEME 30

approach differs from their earlier method where the 2-aryltetralone intermediate formed by the $S_{RN}1$ mechanism was the precursor to ring C formation (Scheme 23). The appropriate two-carbon unit necessary for ring B formation was incorporated in the nucleophilic enolate *o*-acetylhomoveratric acid **210** in order to produce a C-2′ functionalised 3-arylisoquinoline intermediate. $S_{RN}1$ reactions between the dimethoxy-substituted *o*-iodobenzamides **208,209** and *o*-acetylhomoveratrylic acid **210** gave the expected intermediates **211,212** in yields of 65–75%. The carboxylic acids were converted *in situ* to the methyl esters of the *N*-methyl-3-arylisoquinolinones **211,212** by methylation with methyl iodide, followed by reduction to the primary alcohols **213,214** with lithium aluminum hydride. The oxidation of this functionality to the corresponding aldehyde with pyridinium chlorochromate caused spontaneous ring closure by nucleophilic attack of the enamine to produce the 2,3,8,9- and 2,3,7,8-oxygenated benzo[*c*]phenanthridin-6-ones **215,216.**

Lete and co-workers have also utilized a 3-arylisoquinolone intermediate as the basis for the synthesis of 6-methylbenzo[*c*]phenanthridines (94T2207). The overall strategy involved the synthesis and intramolecular cyclization of appropriately functionalized *N*-1,2-diarylethyleneamides (prepared from deoxybenzoins), which could be cyclized under Bischler–Napieralski conditions to 3-arylisoquinolinium salts. This approach involved the synthesis of a deoxybenzoin precursor with an appropriate functionality, which would ultimately be used in the formation of ring B. The deoxybenzoin **219** was initially obtained by a Friedel–Crafts reaction between homoveratryl chloride **217** and 1,2-dimethoxybenzene **218** in the presence of tin(IV) chloride, followed by treatment with LDA and alkylation with allyl bromide to yield the functionalized deoxybenzoin precursor (71T3495) (**220**) (Scheme 31). Stoichiometric amounts of benzylamine (chosen because it could be easily removed under nonhydrolytic conditions), the deoxybenzoin **220** and titanium(IV) chloride produced the imine **221,** which reacted with acetyl chloride in the presence of $TiCl_4$, to give the *Z*-enamide **222** exclusively in 90% yield. Treatment of the *Z*-enamide under Bischler–Napieralski conditions ($POCl_3$ in acetonitrile, reflux) gave the 3-arylisoquinolinium salt **223** in 93% yield, which cyclized quantitatively to the 6,12-dimethyl-substituted dihydrobenzo[*c*]phenanthridine **224.**

Using the Bischler–Napieralski cyclization of enamides, the same group (94TL2973) was able to synthesize 11-acetoxy-6-methyl benzo[*c*]phenanthridines by following a variation on the route just described. The strategy was to attach the functionality for ring B formation onto what would be ring A of the final tetracyclic system, i.e., to produce a C-2′-substituted 3-arylisoquinoline intermediate, thereby directing cyclization with the isoquinoline moiety as the final step (cf. 92T8285). This was in contrast to their



SCHEME 31

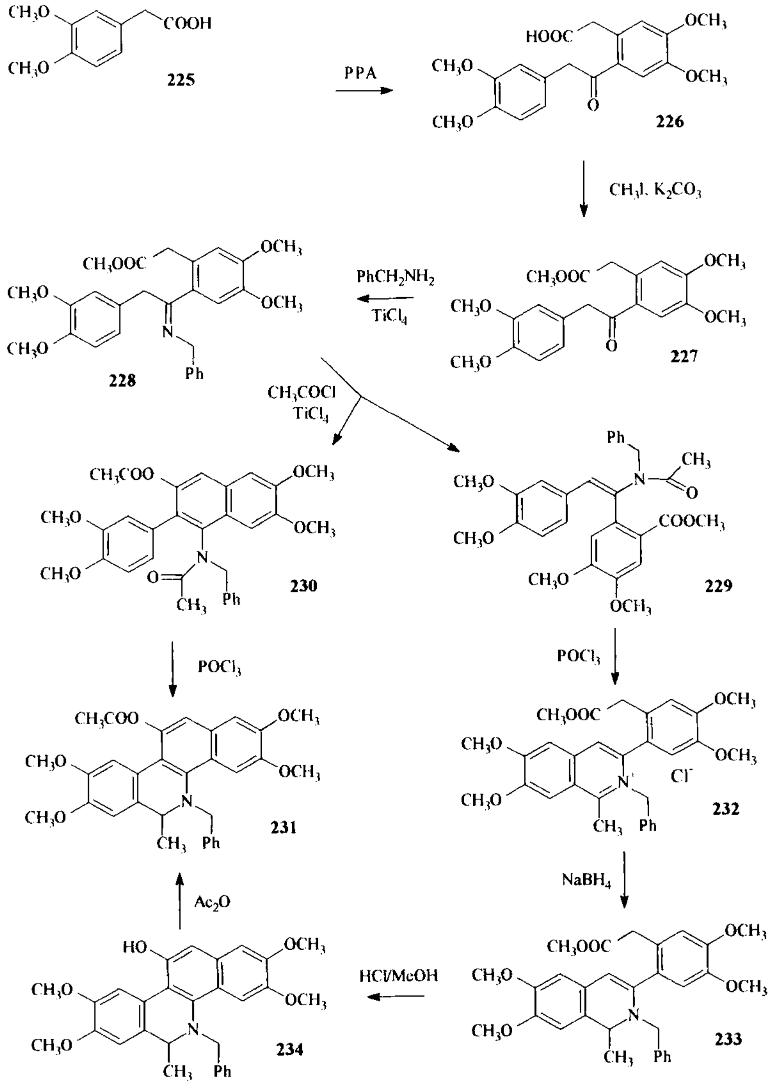
earlier approach, where such a functionality was in the 4 position of the isoquinoline moiety itself and cyclization with the C-2′ position of the 3-aryl group was the last step. Synthesis of the C-2′-substituted 3-arylisoquinoline intermediate first required production of the keto acid **226,** prepared by intermolecular acylation of 3,4-dimethoxyphenyl acetic acid **225.** Treatment of the corresponding ketoester **227** with benzylamine and $TiCl_4$ under

anhydrous conditions led to the intermediate imine **228,** which on acetylation with acetyl chloride did not produce the expected mixture of *E* and *Z* enamide isomers, but a 1.1 : 1 mixture of the *E*-enamide **229** and the naphthylamide **230** in an overall yield of 60%. The latter was presumed to arise via the initially formed *Z* isomer of the enamide, followed by intramolecular acylation to the naphthol and subsequent acetylation of the hydroxyl group. After separation, the naphthylamide **230** gave the 11-acetoxy-6-methyl benzo[*c*]phenanthridine **231** in 80% yield under Bischler–Napieralski conditions (Scheme 32). Using the same conditions, the *E*-enamide **229** isomerized to the *Z* form, which cyclized to the unstable 3-arylisoquinolinium salt **232** and reduced to the more stable 3-aryl-1,2-dihydroisoquinoline **233** with sodium borohydride. Intramolecular acylation of this enamine (HCl/methanol) gave the 11-hydroxy-6-methyl benzo[*c*]-phenanthridine **234** in 35% yield from the enamide. Because of its rapid decomposition, it was acetylated with acetic anhydride to the 11-acetoxy-6-methylbenzo[*c*]phenanthridine **231** quantitatively (Scheme 32).

By applying the mixture of the *E*-enamide and naphthylamide to the synthetic procedure applied to the naphthylamide alone, the overall yield of the 11-acetoxy-6-methylbenzo[*c*]phenanthridine was considerably improved.

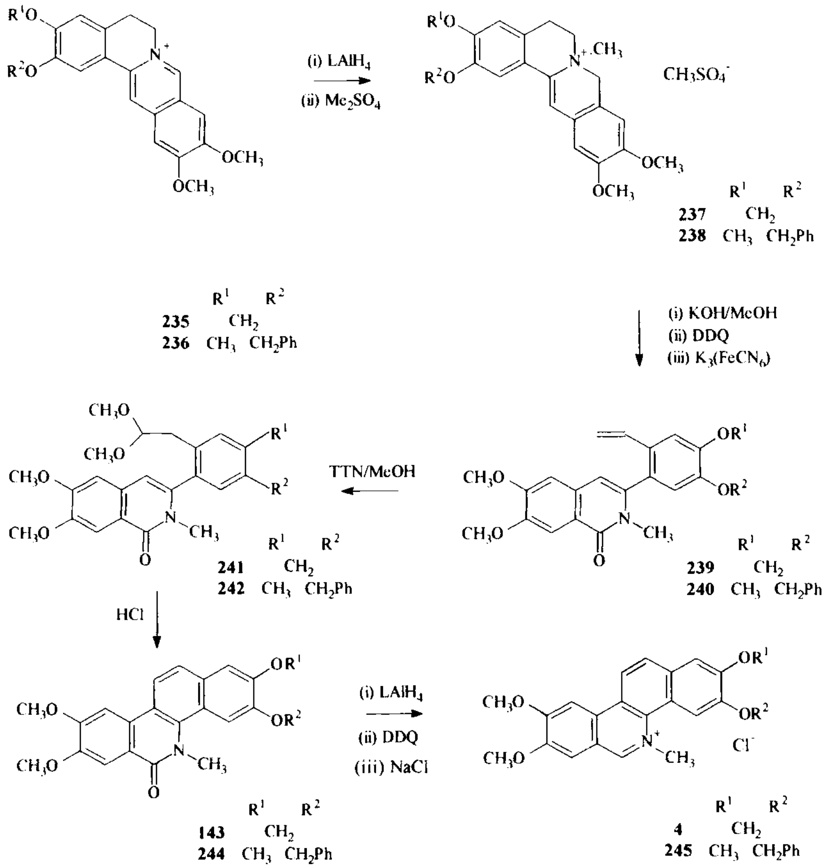
The benzo[*c*]phenanthridines synthesized by Lete's group are not reported to possess any biological activity. Indeed, no 5-benzyl-substituted quaternary benzo[*c*]phenanthridines appear to be active. Their syntheses have been included because of the high overall yields (60%) and particularly their versatility, which allows for the synthesis of C-6 alkyl-substituted benzo[*c*]phenanthridines and the possibility of functionalization at C-11. Coupled with the facile removal of benzyl substituents from isoquinolines, it is envisaged that these routes will offer significant contributions to the structure–activity relationship profiles, which are being compiled for this class of compounds.

The chemical transformation of protoberberine alkaloids to the benzo[*c*]-phenanthridines by Hanoaka *et al.* (87CPB2348) can also be classed as a synthesis involving final ring B closure via a 3-arylisoquinoline intermediate (Scheme 33). The key step is the fission of the C_6—N bond in a 2,3,10,11-oxygenated protoberberine skeleton to afford a labile enamine, which is stabilized by oxidation to the amide. The styrene functionality in the ortho position of the 3-aryl moiety provides the handle for cyclization of ring C via conversion to the acetal. Initially, the appropriately substituted berberine **235,236** is reduced with $LiAlH_4$ to an enamine and subsequently methylated with dimethyl sulfate to yield a quaternary product **237,238.** This undergoes Hoffman elimination in methanolic potassium hydroxide, cleaving the C_6—N bond to the labile enamine, which is stabilized by oxidizing to the amide **239,240** using DDQ and potassium ferricyanide successively.



SCHEME 32

Treatment with thallium(III) trinitrate (TTN) in methanol affords the acetal **241,242,** which undergoes hydrolysis, cyclization, and dehydration on addition of 10% hydrochloric acid to oxynitidine **143** or *O*-benzyloxyfagaronine **244.** Successive reduction with $LAlH_4$ and oxidation with DDQ produces



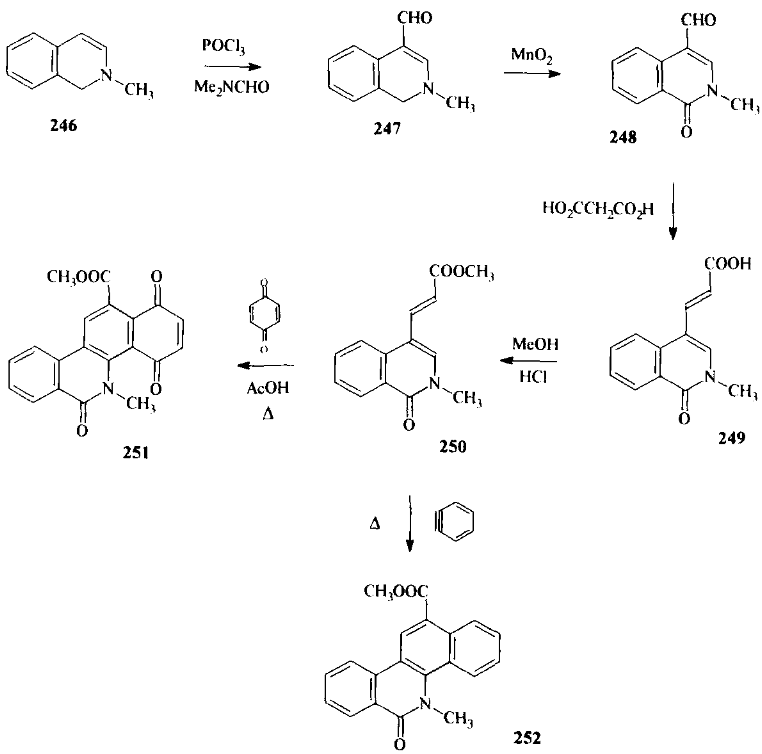
SCHEME 33

nitidine **4** or *O*-benzylfagaronine **245** via the dihydrobenzo[*c*]phenanthridines in overall yields of 23 and 30%, respectively. Debenzylation to fagaronine with acid was achieved in 97% yield. Using a similar approach, the same group obtained sanguinarine and a number of hexahydro and tetrahydro nonquaternary benzo[*c*]phenanthridines from the 2,3,9,10-oxygenated protoberine alkaloid coptisine (86CL739).

2. *Syntheses via the Isoquinoline Intermediate*

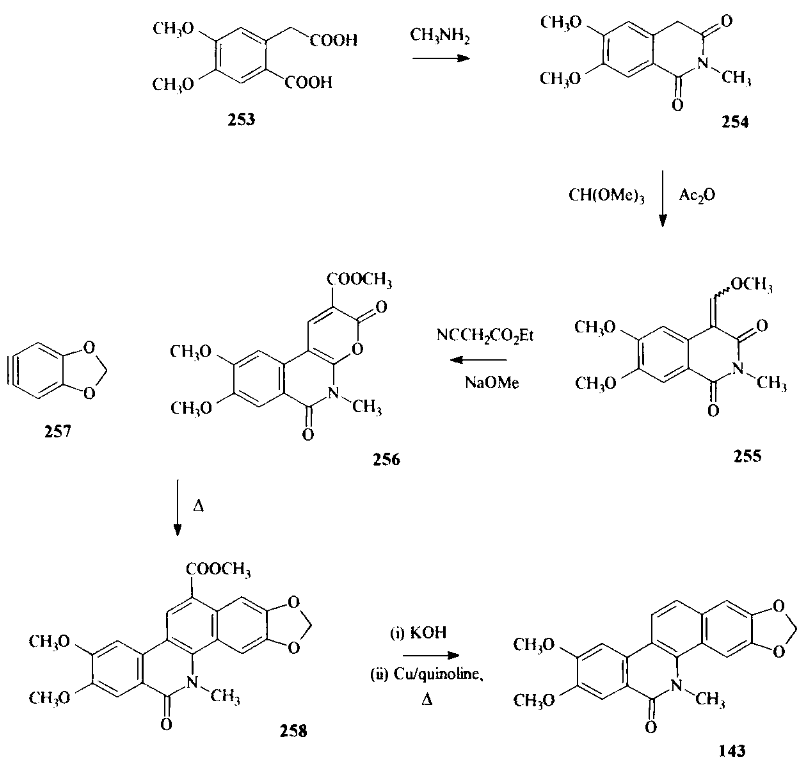
In addition to developing a route in which ring C was formed by cycloaddition of an azadiene and an aryne (86JOC2718; 87TL2407; 92JOC5907)

(Scheme 22), Castedo and co-workers applied the Diels–Alder strategy to the development of a convergent benzo[*c*]phenanthridine synthesis in which the final step involved the formation of ring B and A from an isoquinolinone intermediate (92JOC5911). They based their work on Dyke's exploration of the applicability of 4-vinylisoquinoline derivatives to Diels–Alder reactions (70T5969). Dyke *et al.* had used the Vilsmeier reaction to prepare 2-methyl-4-formyl-1,2-dihydroisoquinoline **247** from 2-methyl-1,2-dihydroisoquinoline **246**, which was subsequently oxidized to 2-methylisocarbostyril-4-aldehyde **248** with manganese dioxide. Reaction with malonic acid produced the β-[4-(2-methylisocarbostyryl)]acrylic acid **249**, followed by esterification with methanol, which yielded the methylacrylate **250** to be used as the diene in the Diels–Alder reaction (Scheme 34). Reaction with an excess of the dienophile-*p*-benzoquinone produced the tetracyclic adduct **251** in 60% yield; however, with benzyne, only 1.2% of the benzo[*c*]phenanthridin-6-one **252** could be isolated.



SCHEME 34

The strategy of Castedo and co-workers was based on the more suitable α-pyrone dienes, which were known to react with benzyne to give an adduct which loses carbon dioxide by a retro-Diels–Alder reaction to afford naphthalene (62CB2718), to obtain the tetracyclic benzo[*c*]phenanthridines by preparing a tricyclic pyrone as the diene intermediate from a 1,3-isoquinolinedione. Reaction of 4,5-dimethoxyhomophthalic acid **253** with methylamine gave the *N*-methyl-6,7-dimethoxy-1,3-isoquinolinedione **254,** which converted to the enol ether **255** in the presence of trimethyl orthoformate and methanol. Sodium methoxide and ethyl cyanoacetate gave the tricyclic pyrone **256,** the diene intermediate, which was then reacted with an excess of 4,5-methylenedioxybenzyne **257** in dioxane to produce the 12-acetoxynitidine precursor **258** in 72% yield. Hydrolysis of the ester and decarboxylation with Cu/quinoline afforded oxynitidine **143** in 72% yield (Scheme 35).



SCHEME 35

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Acyclonucleosides: Part 1. *Seco*-Nucleosides

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I. Introduction

This chapter is the first of a sequence of three chapters that will appear in successive volumes of this series dealing with the chemistry of acyclonucleosides. Acyclonucleosides are a group of nucleosides that differ from the parent ribonucleosides only by the absence of the ring structure of the pentosyl residue. The general feature of the important members of this class of nucleosides is the absence of one or more of the bonds of the pentose moiety to give an open-chain residue (i.e., they possess portions of the pentose residue). Those nucleosides missing one bond of the furanosyl residue are called *seco*-nucleosides. The terms *diseco-*, *triseco-*, *tetraseco-*, and *pentaseco*-nucleoside are given through this series of chapters to indicate the number of missing bonds in the respective acyclonucleoside. Also included under this class of nucleosides are those heterocycles that are attached to open-chain carbohydrate residues. The objective of this series

of three chapters is not to present an exhaustive review, but rather to categorize the various types of acyclonucleosides and to discuss the methods for the synthesis of each type. The present chapter deals with *seco*-nucleosides (one bone disconnection), whereas the second in the series will cover *diseco*-nucleosides, and the final chapter of the series will deal with *tri-*, *tetra-*, and *pentaseco*-nucleosides.

The chemistry and antiviral activities of acyclonucleosides were reviewed in 1986 (86JHC289). Reviews covering only parts of their biochemical aspects, particularly those related to the potent antiviral agent acyclovir, as well as those acting as inhibitors of HIV replication, have been published (86CS113; 89YGK694; 90MI2; 93MI1). Chemotherapy of acquired immunodeficiency syndrome (AIDS) using acyclic nucleoside phosphonate analogues was reviewed (91MI2). A bibliography of acyclic nucleosides was also reported (85MI2). However, the literature in this area is increasing and much attention has been devoted to the synthesis, as well as to the biological activities of acyclonucleosides, as a consequence of the presence of potent highly selective antiherpetic activity for some of their members. This led to a diversity of structures of either of the lead compounds or their analogues, with many variations in order to enhance their biological activity and their selectivity, or to lower their toxicity. This chapter gives the general scope of the subject.

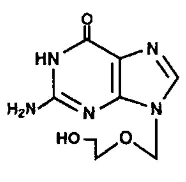
The lead compounds are acyclonucleosides that show highly potent therapeutic activity and/or antibiotic qualities. A molecular modeling study of nucleoside analogues as potential anti-AIDS drugs was reported (91MI3). Calculated conformational properties were used to compare the active and nonactive compounds (88MI1). The conformations of acyclobenzimidazole nucleoside analogues were determined by means of NMR spectroscopy [84MI1; 88ZN(C)231; 90ZN(C)915]. Although it is expected that the flexibility of acyclic chains of acyclonucleosides would lead to equilibrium mixtures of conformers in solution, they are capable of adopting conformations resembling a portion of the pentose rings, a factor that plays a role in their biological activities (85CJC1215).

The differentiation of anomeric acyclonucleosides by FAB tandem mass spectrometry was reported (90MI1; 91MI10). Regioisomeric compounds could be differentiated by kinetic energy release measurements [87-AQ(C)271; 91RCM72]. Electronic structure, spectral properties, and acid–base and tautomeric equilibria of some adenosine acyclo derivatives were investigated (89MI5).

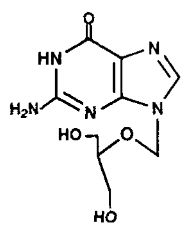
The potent antiherpetic drug 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir, Zovirax) (78NAT583) possesses potent antiviral activity in cells infected with herpes simplex virus type 1 (HSV-1), but it is essentially nontoxic to uninfected host cells. The discovery of acyclovir (ACV) has

stimulated extensive research in the synthesis of new acyclonucleosides in which the carbohydrate moieties are acyclic chains mimicking the sugar portion of naturally occurring nucleosides. Thus, they have long been considered potentially capable of interfering with the activity of various enzymes for which the natural nucleosides serve as substrates.

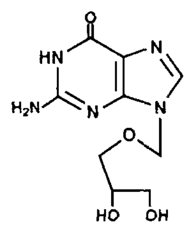
Subsequent members of this class include the exceptionally potent and broadly active 9-[(1,3-dihyroxy-2-propoxy)methyl]guanine or 2′-nor-2′-deoxyguanosine (2′NDG, BIOLF-62, BW-759u, DHPG), which was found to be effective against not only simplex virus types 1 and 2, but also cytomegalovirus (HCMV), 1 Varicella-Zoster, and Epstein-Barr virus (83AAC676, 83PNA2767). It has a superior activity to that of acyclovir. Other members were also reported, e.g., (*R*)-9-[3,4-dihydroxybutyl]guanine (DHBG, buciclovir), 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (2HM-HBG), (*S*)-9-[(2,3-dihydroxypropoxy)methyl]guanine [(S)-INDG] (DHPMG), 3-hydroxypropyladenine (DHPA), and 2,3-dihydroxypropyluracil (DHPU). Further modifications led to groups of compounds of particular interest. Thus, modification on the heterocyclic ring led to HEPT analogues. Modifications on the side-chain were also investigated. Thus, *erythro*-9-(2-hydroxy-3-nonyl)adenine (EHNA) was reported as an ADA inhibitor.



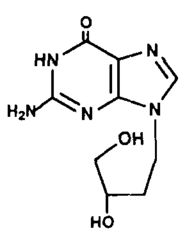
ACV



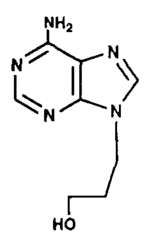
DHPG



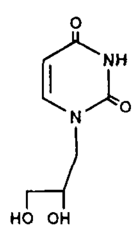
DHPMG



DHBG



DHPA



DHPU

SCHEME 1

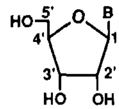
Acyclonucleosides with and without hydroxyl group on the side-chain are prepared to recognize the role of phosphorylation. However, phosphoryl derivatives and their respective nucleotides are not considered here.

The syntheses of acyclonucleosides mostly involve alkylation of the heterocyclic rings and to a lesser extent construction of the heterocyclic ring onto the polyol. As a consequence of the diversity of structures and considering the main features of acyclonucleosides, the acyclic nature of the sugar or side-chain part, it is more convenient to arrange them according to the aglycone rather than the heterocyclic rings. Their arrangement is conveniently done by considering the possible disconnections on the basic structure of the ribofuranosyl base. Accordingly, there are five possible groups resulting from the disconnection of one, two, three, four, and five bonds. The first group, termed *seco*-nucleosides, contains five categories or types of structures (1.1–1.5); the second group, termed *diseco*-nucleosides, contains seven categories (2.1–2.7); the third group, termed *triseco*-nucleosides, contains four categories (3.1–3.4); the fourth group, termed *tetraseco*-nucleosides, contains three categories (4.1–4.3); and the fifth group, termed *pentaseco*-nucleosides, contains two categories (5.1 and 5.2). The last two groups included numerous simple alkyl or hydroxyalkyl derivatives of heterocyclic rings which are not included here. The literature cited here was searched up to Volume 119 of *Chemical Abstracts* on acyclonucleosides. The structural formulas in Scheme 2 have been depicted in a ribose-like conformation in order to draw attention to their similarity to the natural nucleosides. The structures do not indicate the chirality of the particular atoms. The chirality may be realized from the mode of synthesis and/or the starting material used in this respect. The letter X in the formulas could be O, S, or CH_2.

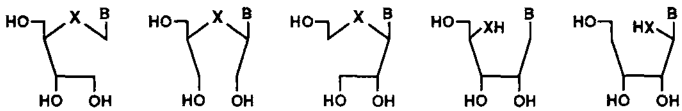
In spite of the different categories in the scheme, the diversity of structures of acyclonucleosides led to other categories that do not fit exactly with those in Scheme 2. However, they were correlated with those in the scheme by considering one of the structures in Scheme 2 as a basic skeleton and the extra groups or chains as substituents. Functional groups other than the hydroxyl can be considered as substituents. The first category in each disconnection represents the most important member.

II. *Seco*-Nucleosides from One Bond Disconnection

Disconnection of one of the bonds of the furanosyl residue is considered. Disconnection between C-4 and C-5 is not considered, as it would afford a tetrafuranosyl nucleoside.

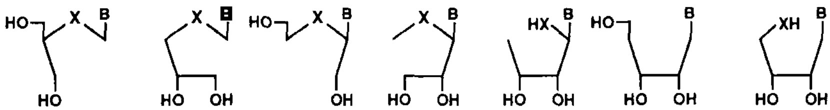


1. Seco-nucleosides from one bond disconnection



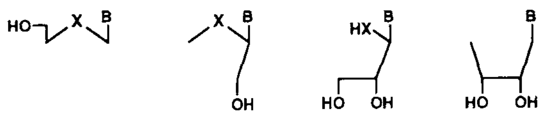
1.1 1.2 1.3 1.4 1.5

2. Diseco-nucleosides from two bond disconnections



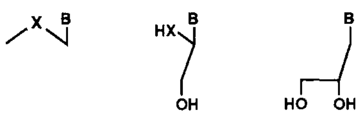
2.1 2.2 2.3 2.4 2.5 2.6 2.7

3. Triseco-nucleosides from three bond disconnections



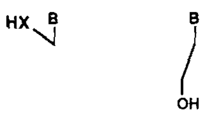
3.1 3.2 3.3 3.4

4. Tetraseco-nucleosides from four bond disconnections



4.1 4.2 4.3

5. Pentaseco-nucleosides from five bond disconnections



5.1 5.2

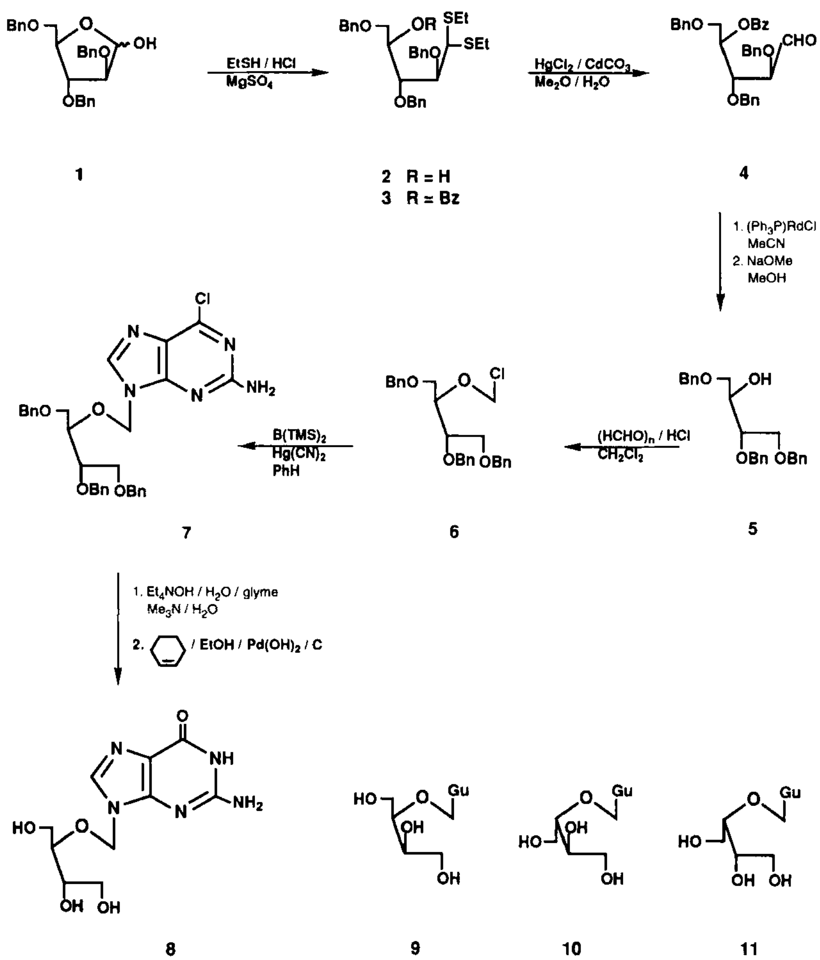
X = O, S, or CH_2

SCHEME 2

A. 1′,2′-*Seco*-NUCLEOSIDES (TYPE 1.1)

1. *General Methods for Construction*

The chiral precursors for this type of nucleoside can be prepared from monosaccharide derivatives. Thus, the synthetic sequence started with 2,3,5-tri-*O*-benzyl-D-arabinose **1** by conversion into the diethylthioacetal **2** followed by benzoylation of the 4-position to give **3**. Decarbonylation of **4**



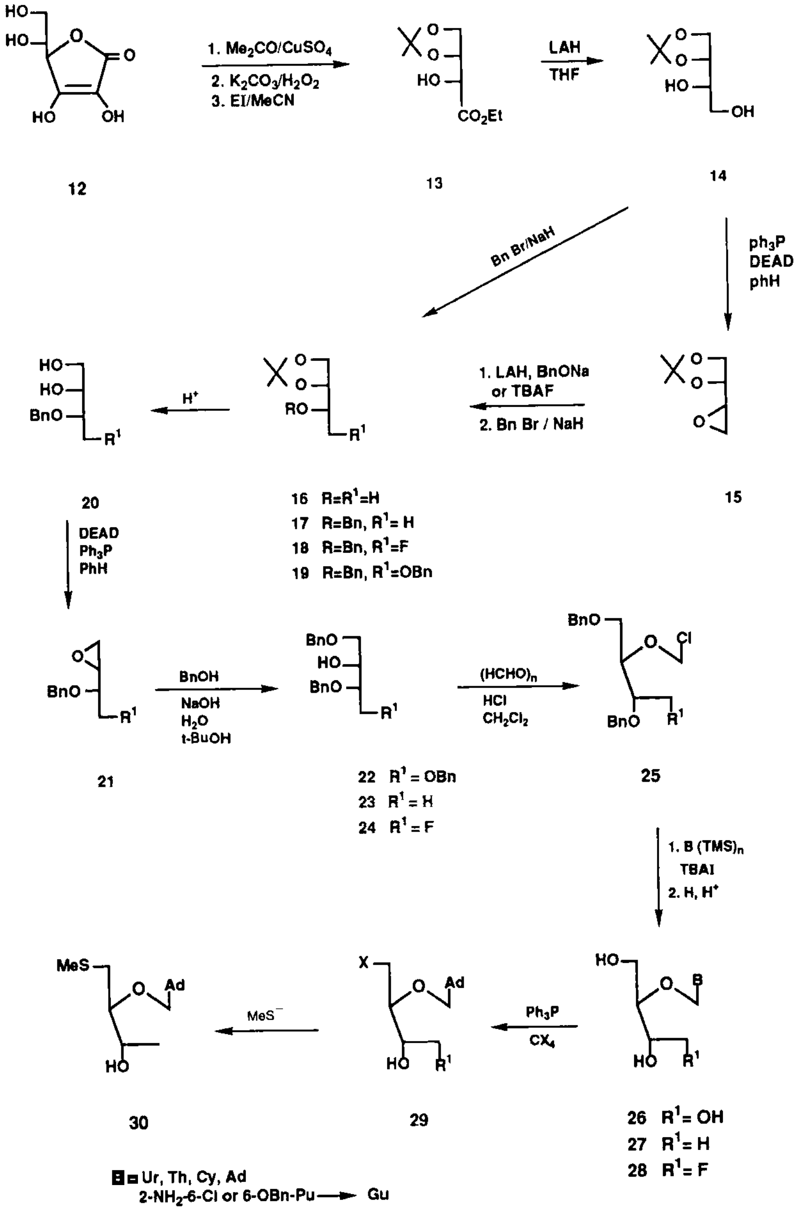
SCHEME 3

and then debenzoylation gave **5**, whose chloromethylation gave **6** (85TL4287). The latter was used in the alkylation of the trimethylsilylated 2-amino-6-chloropurine to give **7**. Hydrolysis and deprotection gave **8** (85TL4287). Isomers **9**, **10**, and **11** were prepared similarly.

Another synthesis of the chiral synthon **25** or its deoxy analogue started from selectively protected butanetriols and butanetetrols prepared from D-isoascorbic acid **(12)** (88JOC2598; 89SC3077; 91JOC4653). Isopropylidenation followed by oxidation with hydrogen peroxide and then esterification gave **13**. Reduction of **13** gave **14**, which was converted to the oxirane **15**. Opening of the ring followed by benzylation or benzylation of **14** gave **16–19**. Acid hydrolysis of **17–19** gave **20**. Epoxide formation gave **21**, whose opening gave **22–24**. Chloromethylation of **22–24** gave **25**, whose reaction with the persilylated uracil or 2-amino-6-chloropurine in presence of tetrabutylammonium iodide afforded the corresponding 1′,2′-*seco*-uridine (and a small amount of the N-3 isomer) and purine (and a small amount of the N-7 isomer), respectively. A mixture of the latter 7- and 9-isomers rearranged exclusively to the 9-isomer on heating. Debenzylation by hydrogenation over Pearlman's catalyst and hydrolysis of the 6-chloropurine derivative gave **26–28**. However, the guanosine analogue could be prepared by reaction of **25** with the sodium salt of 2-NH_2-6-OBn-purine followed by deprotection (89MI7, 89MI8; 90JMC681). Halogenation of **27** or **28** gave **29** (89MI8). The respective 5-bromide could be displaced with potassium methyl mercaptide to give **30**. Compounds were tested as inhibitors of mammalian methylthioadenosine phosphorylase.

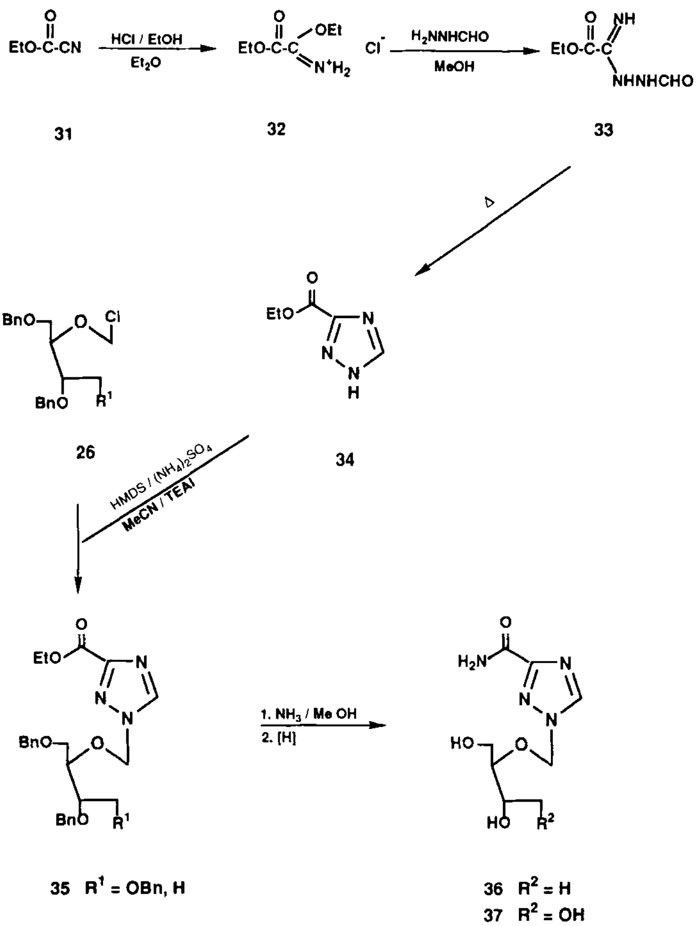
The ribavirin analogues **36** and **37** were prepared by the conversion of ethyl cyanoformate **31** to ethyl carboethoxyformimidate **32**, whose reaction with formylhydrazine gave **33**, which then thermally cyclized to **34**. Coupling this synthon with the protected chiral chloromethyl ethers of 1,3-di-*O*-benzylbutane-1,2*R*,3*S*-triol and 1,3,4-tri-*O*-benzylbutane-1,2*R*,3*S*,4-tetrol **26** gave **35**. The ester function was converted to the carboxamide moiety, and the side-chain was deprotected to give the 1′,2′-*seco*-nucleosides **36** and **37** (88JHC651).

The protected acetoxymethyl ether **38** can be used directly, avoiding the preparation of the corresponding halomethyl ether, whereby the amino group of the nucleosides needs no protection. Coupling acetyl derivative **38** with 2-nitroimidazole **39** followed by deacetylation with triethylamine in aqueous methanol gave **40** (91MIP1), which has a radiosensitizing effect and high safety. It is useful in the radiotherapy of cancers. Similarly, the protected acetoxymethyl esters of L-threitol **41** were reacted with silylated nucleobases under phase transfer conditions to give **42** (89TL6165). Debenzoylation gave the corresponding hydroxy compounds **43**. In the case of the guanine derivative, equal amounts of N-9 and N-7 were obtained.



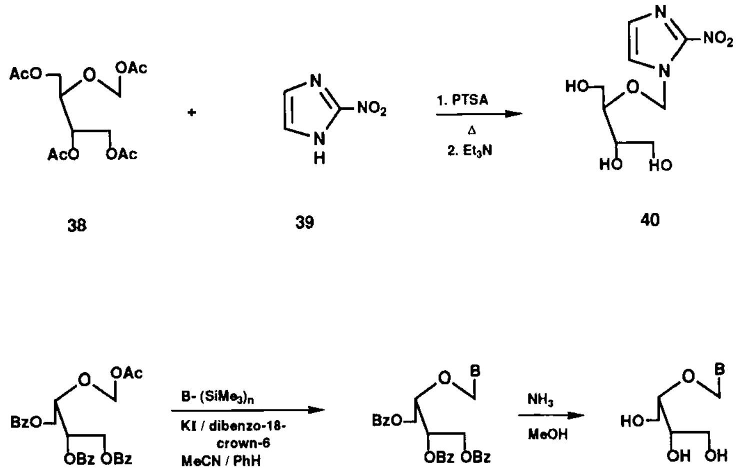
12
1. Me2CO/CuSO4
2. K2CO3/H2O2
3. EI/MeCN
13
CO2Et
LAH
THF
14
Bn Br/NaH
ph3P
DEAD
phH
15
1. LAH, BnONa
or TBAF
2. Bn Br / NaH
H+
20
16 R=R1=H
17 R=Bn, R1= H
18 R=Bn, R1=F
19 R=Bn, R1=OBn
DEAD
Ph3P
PhH
21
BnOH
NaOH
H2O
t-BuOH
22 R1 = OBn
23 R1 = H
24 R1 = F
(HCHO)n
HCl
CH2Cl2
25
1. B (TMS)n
TBAI
2. H, H+
26 R1= OH
27 R1= H
28 R1= F
Ph3P
CX4
29
MeS−
30
B = Ur, Th, Cy, Ad
2-NH2-6-Cl or 6-OBn-Pu → Gu

SCHEME 4



SCHEME 5

The cleavage of the benzyl ether groups was usually accomplished by catalytic hydrogenation. The relative reaction rates were dependent on the hindrance around the benzyl groups (86MI1). Catalytic transfer hydrogenation was preferred when the benzyl group was highly hindered. In the case of the compounds containing an aliphatic NH_2 group, $PdCl_2$ was used as a catalyst instead of Pd/C.



38 39 40

41 42 43

B = Ad, Cy, Gu, Th

SCHEME 6

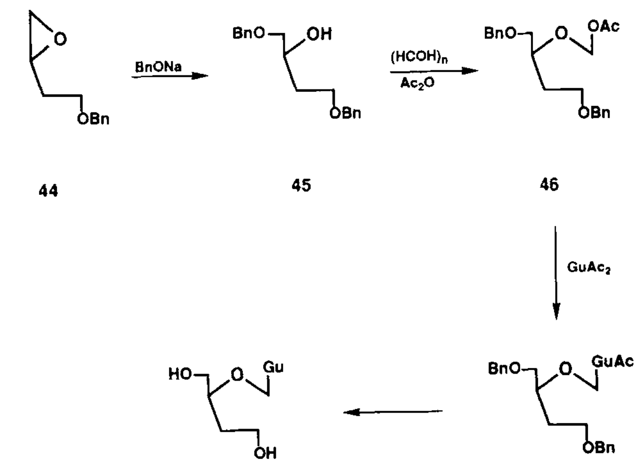
2. *Deoxy and Deoxyazido Analogues*

Alcohol **45** was synthesized by treatment of 4-benzyloxy-1-butane oxide **44** with sodium benzyloxide, then converted to the acetoxymethyl ether **46,** which condensed with diacetylguanine to give **47,** whose deprotection gave **48** (86JMC1384). It is less active than DHPG against HSV-1.

The (*S*)-*O*-benzylglycidol **49** with MeMgCl gave **50,** whose chloromethylation gave **51,** which reacted with base to give **52.** Hydrolysis or amination of the 6-chloropurine derivatives gave the respective Gu, Inos, and Ad analogues. Debenzylation gave **53** (89JMC76; 91MI12).

The 1′,2′-*seco*-AZT **55** and its 3′*R*,4′*S* diastereomer **57** were prepared from coupling of thymine with **54** and **56,** respectively, followed by deprotection, tritylation, azido formation via a Mitsunobu reaction, and detritylation. The chiral acyclic side chains were derived from D-isoascorbic acid (92MI1).

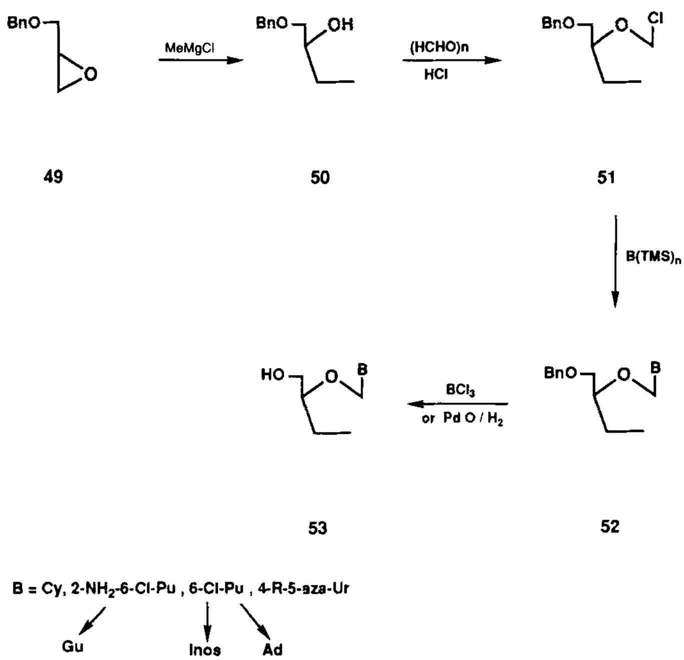
The incorporation of a cyclopropane moiety into the acyclic chain may impose a constraint on its flexibility that could result in a better conformation for enzyme interaction (88JMC2304). Thus, the racemic 1′,2′-*seco*-



44 45 46

48 47

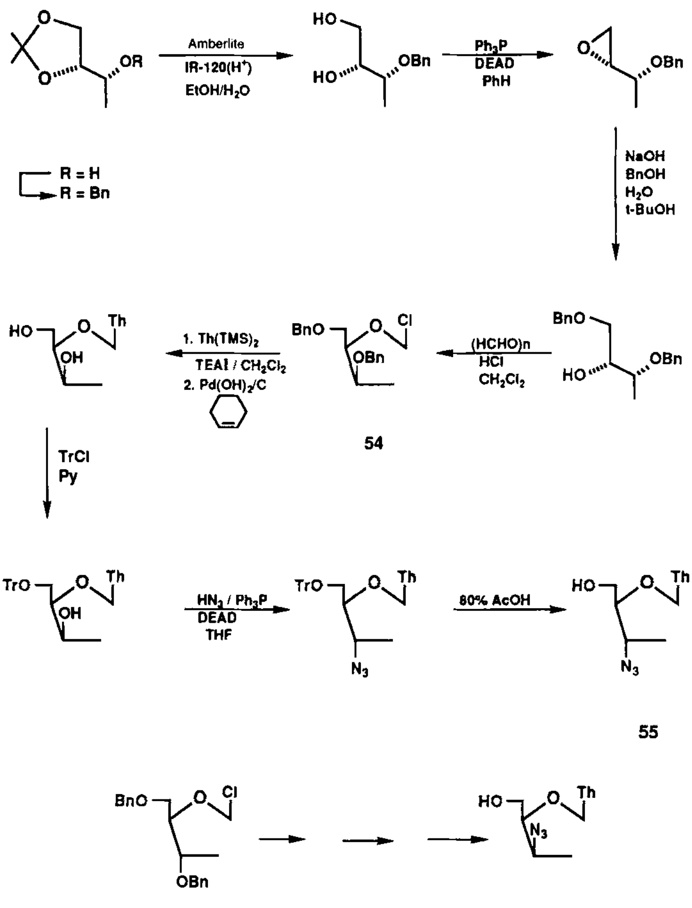
SCHEME 7



49 50 51

53 52

SCHEME 8

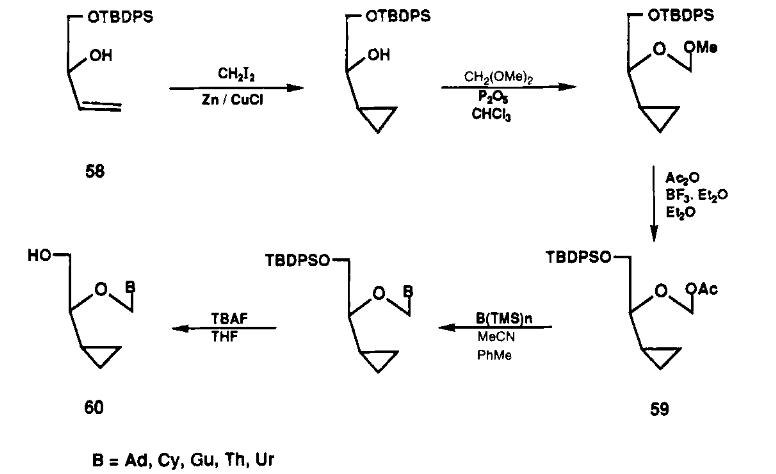


SCHEME 9

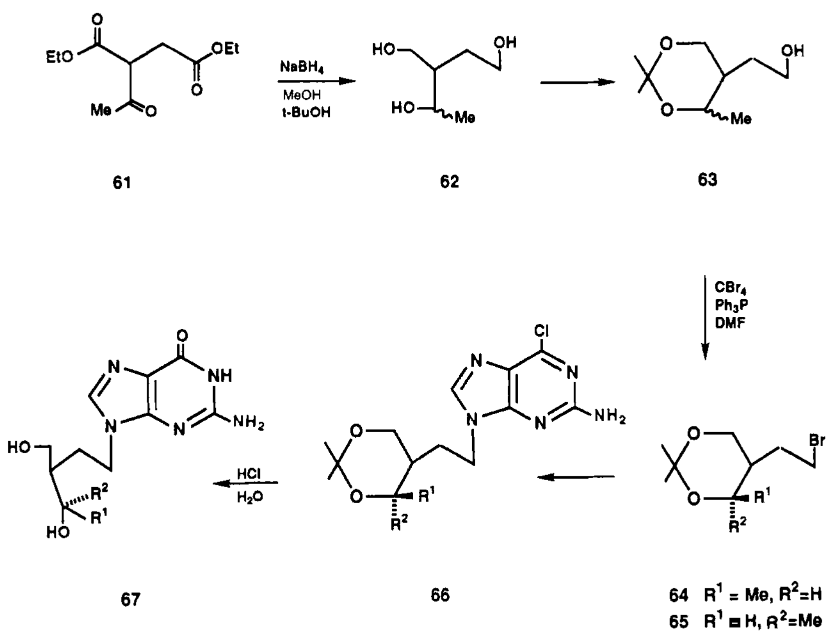
2′,3′-methanonucleoside **60** was synthesized from olefin **58** via its transformation to **59**, which upon coupling with base and deprotection gave **60** (92SC1115). None of these had any effect against DNA or RNA viruses in cell cultures.

3. *Carboacyclic Analogues*

The carboacyclic nucleoside analogues were prepared from diethyl acetylsuccinate **61** by reduction to triol **62**, whose isopropylidenation gave



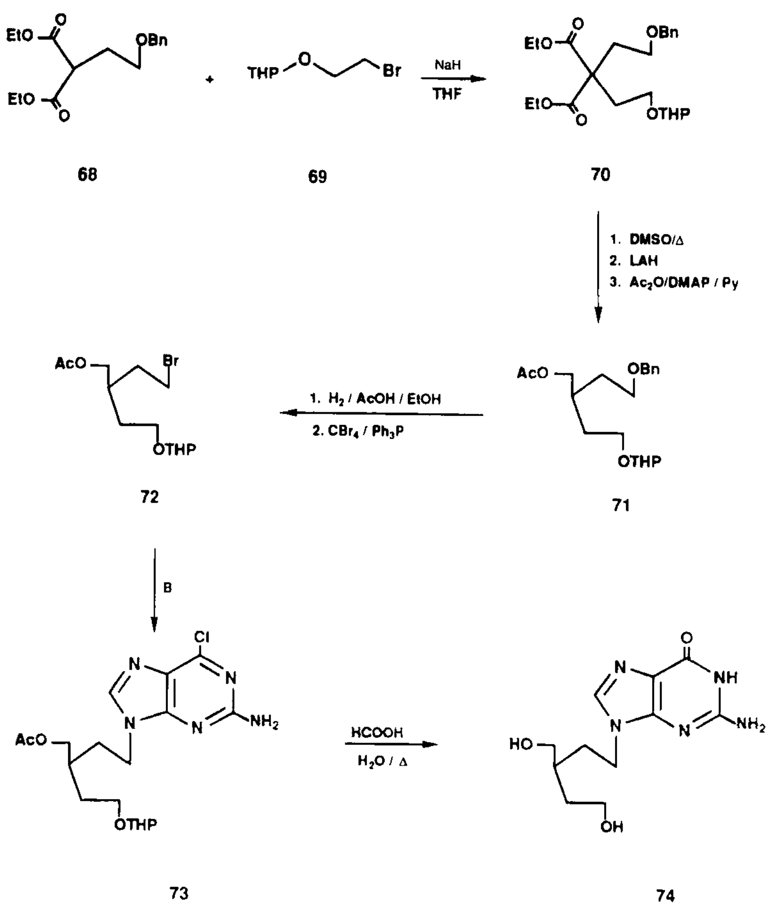
SCHEME 10



SCHEME 11

63. After bromination and separation into **64** and **65**, each was used to alkylate 2-amino-6-chloropurine to give **66**, whose hydrolysis gave **67** [88JCS(P1)2777]. They showed weak anti-herpes-virus activity.

The synthesis of the analogue **74** commenced from the malonate derivative **68**. Alkylation of **68** with tetrahydropyranyl bromoethanol **69** gave **70**, which was decarboxylated followed by reduction and acetylation to give **71**. Hydrogenolysis of the latter, followed by bromination, gave **72**. Alkylation of the purine derivative gave **73**, which was deprotected to **74** [88JCS(P1)2777]. It showed weak anti-herpes-virus activity.



SCHEME 12

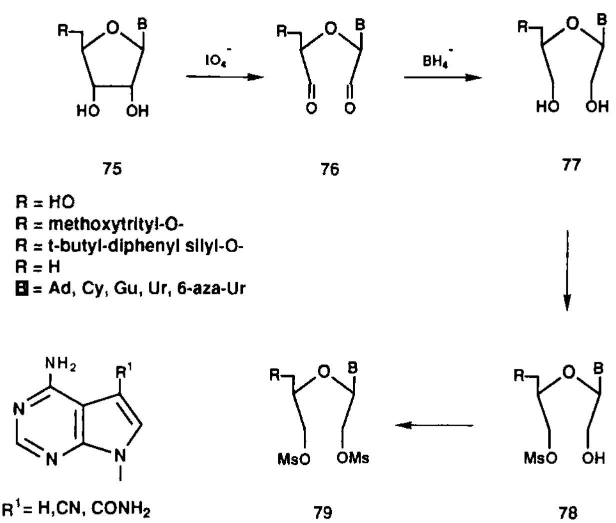
B. 2′,3′-*Seco*-Nucleosides (Type 1.2)

1. *General Methods for Construction*

The strategy used for the preparation of the trihydroxy derivatives of adenosine, guanosine, uridine, 5-ethyluridine, cytidine, and 5,6-dichlorobenzimidazole of type **77** started with **75** using a 1 : 1 mixture of periodate and borohydride supporting resins [83MI1; 85CJC1215, 85TL1305; 86AP360; 91JPP(K)03068564]. The same strategy was also applied to 5′-*O*-protected purineribonucleosides, hypoxanthin-9-yl and adenin-9-yl **75,** where the protecting group was a 4,4′-dimethoxytrityl or a *t*-butyldiphenylsilyl group (88T6419). 5′-Monoethoxytrityl nucleosides were used to provide more easily purified products (85S399). The respective 5′-deoxy guanosine and uridine were also used to prepare the deoxy analogues (86CJC1885; 88KGS91). Tubercidin, toyocamycin, and sangivamycin were similarly treated to give the respective acyclic analogues (89JMC402).

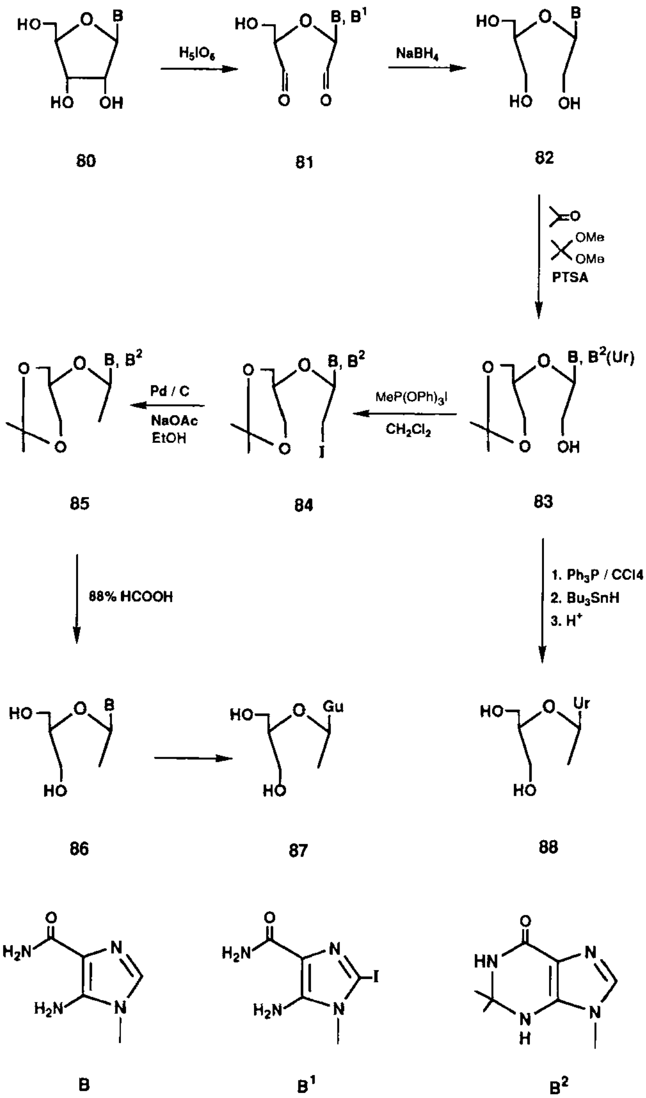
2. *Modified Side-Chain Analogues*

The respective 2′,3′-di-*O*-mesyl derivatives **79** were used to prepare 2′,3′-disubstituted analogues. Because the 2′ position was significantly less reactive than the 3′ position, selective substitution could be achieved to give



Scheme 13

78. Thus, 3′-amino-3′-deoxy-2′,3′-*seco*-adenosine and 3′-deoxy-2′,3′-*seco*-inosine were prepared, and the former was used for the synthesis of a *seco*-puromycin analogue, which was not capable of inhibiting protein synthesis in reticulocyte systems using globin mRNA (88T6419).

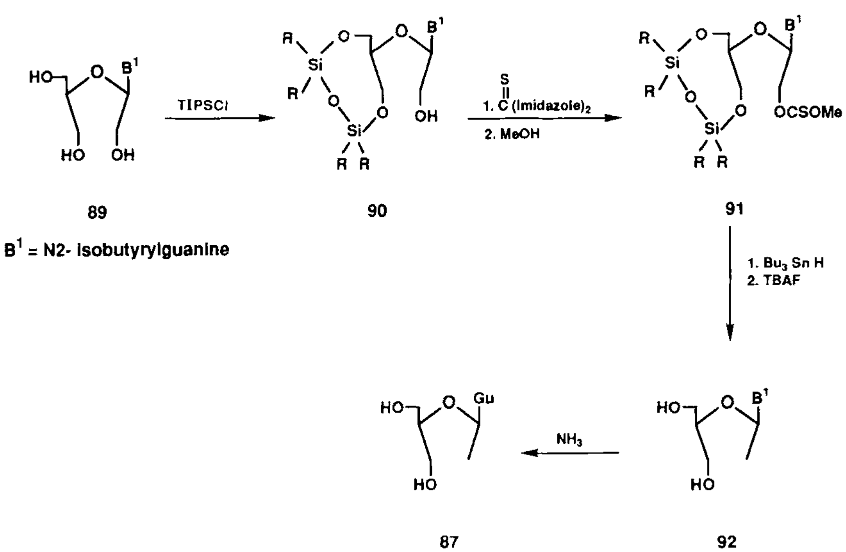


SCHEME 14

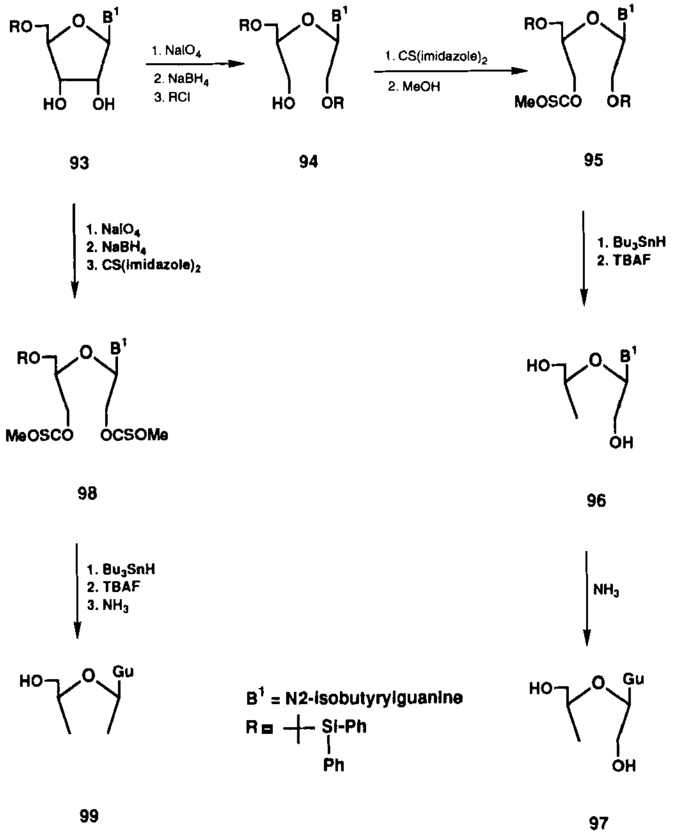
Chiral 2′,3′-*seco*-2′-deoxy nucleosides were conveniently prepared from uridine **75** (R = OH) and its analogue 1-(α-D-*arabino*furanosyl) uracil. The 3′,5′-dihydroxy groups in 2′,3′-*seco*-uridine **77** or **82,** obtained from **76** or **81,** were blocked by an isopropylidene group to give **83;** the hydroxymethyl group was converted to Me by Ph_3P/CCl_4, with subsequent reduction by Bu_3SnH and subsequent deacetalation to give **88** (88KGS822).

Periodate oxidation of **80** afforded **81** (**B,B**[1]). Their reduction afforded **82,** which was converted to the acetonide **83(B)**; prolonged reaction time led to the formation of **83(B**[2]**)**. Treatment of **83** with Rydon's reagent gave the iodomethyl derivative **84,** which was reduced by catalytic hydrogenation to the methyl derivatives **85.** Removal of the isopropylidene group could be accomplished to give **86.** Cyclization of **86** gave the guanine analogue **87** (89MI9). None of these acyclic nucleosides showed activity *in vitro* against herpes viruses HSV-1 and HSV-2. The 2′-deoxy analogue inhibited the increase in the serum DNA of duck hepatitis B virus [91JPP(K)03068564].

An alternative procedure for the synthesis of the 2′-deoxy analogues was also achieved. *N*-2-Isobutyryl-2′,3′-*seco*-guanosine **89,** upon selective protection with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, gave **90.** Deoxygenation of the C-2′ hydroxyl was achieved *via* the formation of the thioester **91,** followed by tributyltin hydride and then deprotection of the hydroxyl groups to give **92,** whose deprotection gave **87** (91MI11). The



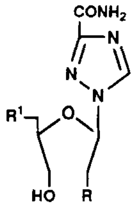
SCHEME 15



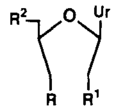
SCHEME 16

other deoxy analogues were prepared by almost the same strategy. Thus, the 5′-*O*-silyl derivative **93** was oxidized and reduced, and then selective protection with *t*-butyldiphenylsilyl chloride gave **94** in addition to the trisilyl derivative. The same strategy of deoxygenation and deprotection used previously was done on the 2′,5′-bis-*O*-silylated alcohol **94** to give **95,** followed by deprotection to **96** and then to the acyclonucleoside **97.** When the same strategy was applied on the bis(methyl thionocarbonate) **98,** the dideoxy analogue **99** was obtained. None of these nucleosides had significant antiherpetic activity.

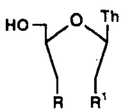
The acyclic analogues **100** and **101** of ribavirin analogues (89MI3; 90MI3), and also those of uridine **102–104,** were prepared (87MI1; 89MI1, 89MI2). Treatment of 2′,3′-*seco*-uridine with the Vilsmeier–Haack reagent gave the



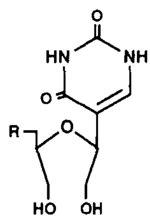
100 R = Br, F, N_3; R^1 = OH
101 R = OH; R^1 = Br, N_3



102 R = R^1 = F, N_3; R^2 = OH
103 R = OH; R^1 = hal., N_3; R^2 = OH
104 R = F, N_3; R^1 = OH; R^2 = OH
105 R = R^1 = R^2 = Cl

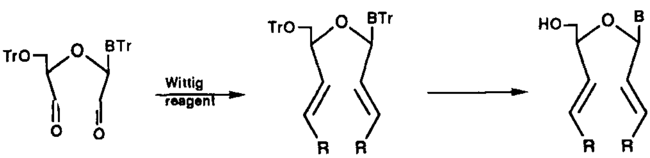


106 R = R^1 = H, OH
107 R = N_3; R^1 = OH
108 R = OH, F, N_3, NH_2 ; R^1 = H



109 R = SH
110 R = NH_2

SCHEME 17

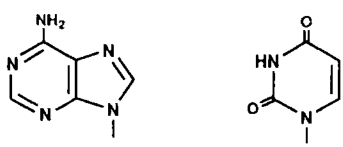


111

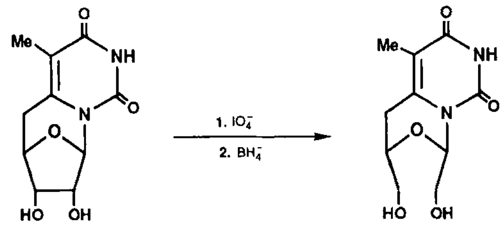
112 R = COOEt
113 R = CN

114

B =



SCHEME 18



115 116

SCHEME 19

2′,3′,5′-trichlorotrideoxy-2′,3′,-*seco*-uridine **105** (88CPB1298). The 2′,3′-*seco*-thymidine derivatives **106–108** were also synthesized (91MI13). The 5′-modified *seco*-pseudouridines **109** and **110** were prepared via the ring cleavage of the sugar moiety (89MI2; 91MI3).

Derivatives from the dialdehydes were prepared by the reaction of **111** with Wittig reagents to give **112** and **113**, whose deprotection gave **114** (82MI2; 85CJC2162). The reaction of 6-azauridine dialdehyde with *N,N*′-diphenylethylenediamine and hydroxylamine gave the bis-imidazolidine and bis-oxime derivatives (83MI1).

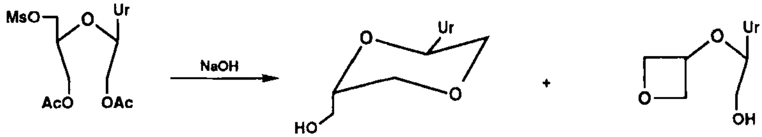
The synthesis of the anti restricted pyrimidine acyclic nucleoside 6,5′-cyclo-5′-deoxy-5-methyl-2′,3′-*seco*-uridine **116** has been achieved by the periodate oxidation and concurrent reduction of **115** (91MI5).

Treatment of **117** with alkali gave **118** in addition to **119** (91TL1821).

C. 3′,4′-*Seco*-Nucleosides (Type 1.3)

1. *General Methods for Construction*

Condensation of the D-ribose derivative **120** with *N*(6)-benzoyladenine in the presence of a catalytic amount of bis(*p*-nitrophenyl)phosphate gave



117 118 119

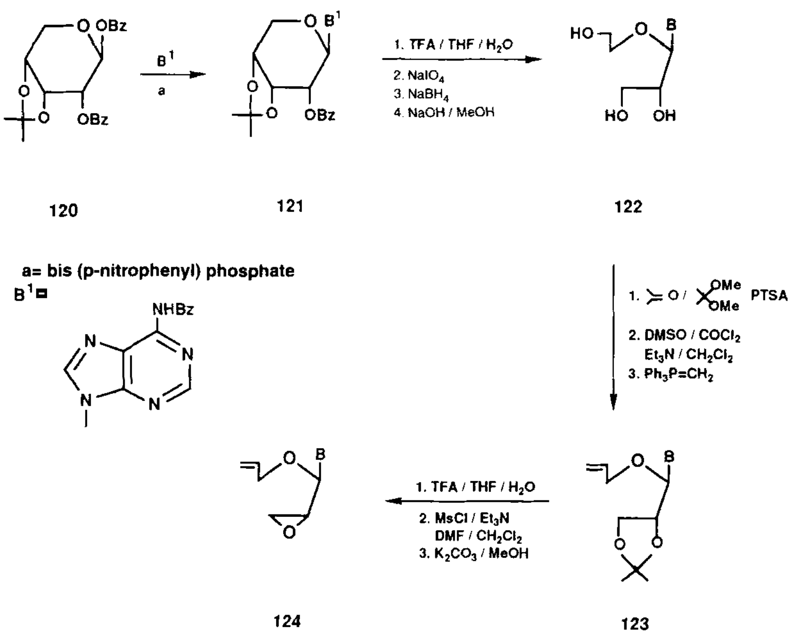
SCHEME 20

121. Removal of the isopropylidene group followed by periodate oxidation gave the dialdehyde, whose reduction and subsequent debenzoylation provided the acyclic triol **122.** The vicinal hydroxyl group was protected as the isopropylidene, and the remaining hydroxyl group was oxidized to the aldehyde followed by a Wittig reaction to give the allylic ether **123.** Hydrolysis of the acetonide followed by monomesylation and then base gave the epoxide **124** (87TL3967).

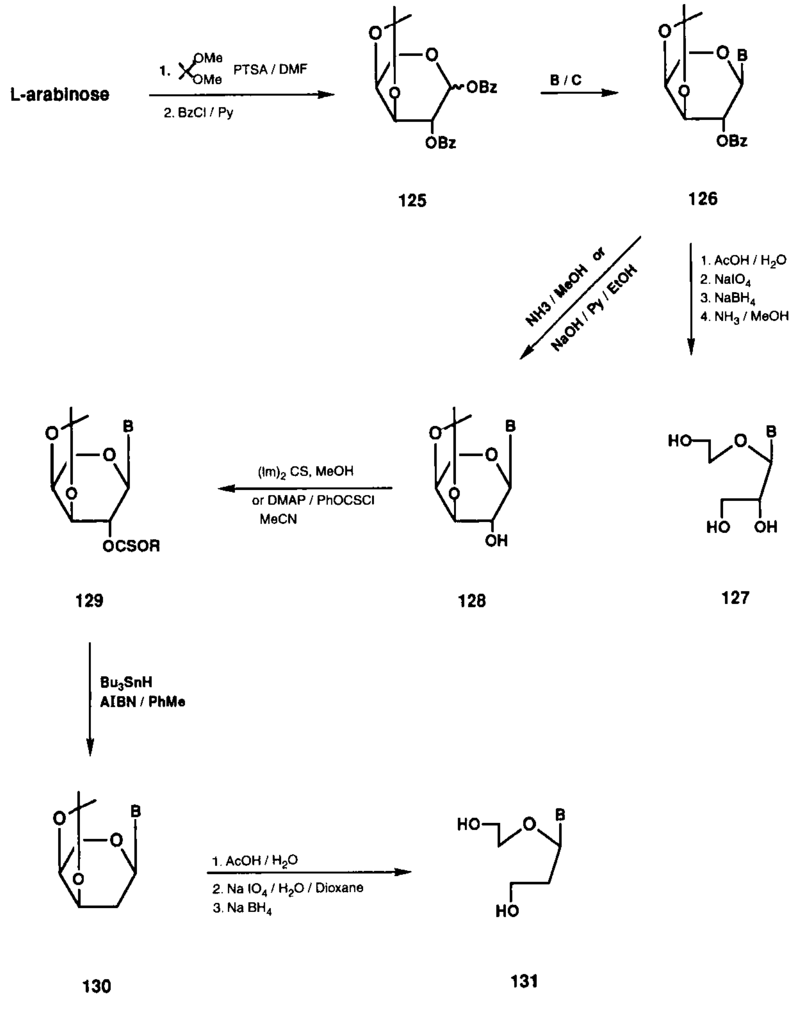
Alternatively, the starting compound could be L-arabinose, which upon isopropylidenation and then benzoylation gave **125.** Glycosylations were effected by various procedures, which, except for the guanine and cytosine series, did not require prior protection of the heterocyclic bases to give **126.** Removal of the isopropylidene and subsequent periodate oxidation, reduction, and then debenzoylation gave the acyclonucleosides **127** [92JCS(P1)1943].

2. *Deoxy Analogues*

The 2′-deoxy analogues **131** were prepared by the debenzoylation of **126** to give **128,** whose deoxygenation was carried out via **129** to give **130.**



SCHEME 21

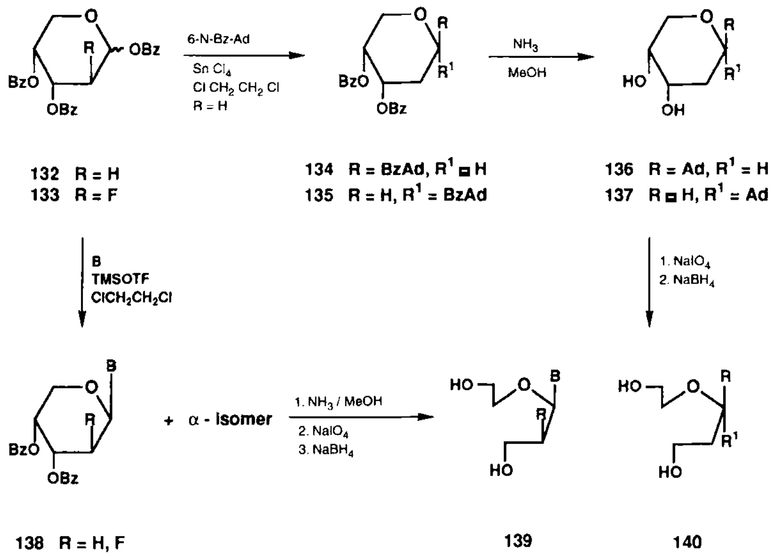


B / C = Ad / Sn Cl_4 / MeCN; 2-N-Palmitoyl Gu / BSA / TMSTF / Me CN
Th or Ur / HMDS / TMSCl / $SnCl_4$ / MeCN; 4-N-Bz-Cy-TMS / TMSTF / Cl CH_2 CH_2 Cl

SCHEME 22

Deisopropylidenation followed by periodate oxidation and reduction gave **131** [92JCS(P1)1943].

The benzoate **132,** obtained from 2-deoxy-D-ribose, was reacted with *N*-6-benzoyladenine by a modified Hilbert–Johnson reaction using $SnCl_4$ to



SCHEME 23

give **134** and **135.** Their debenzoylation gave **136** and **137,** whose periodate oxidation and reduction gave **140** (91T9993).

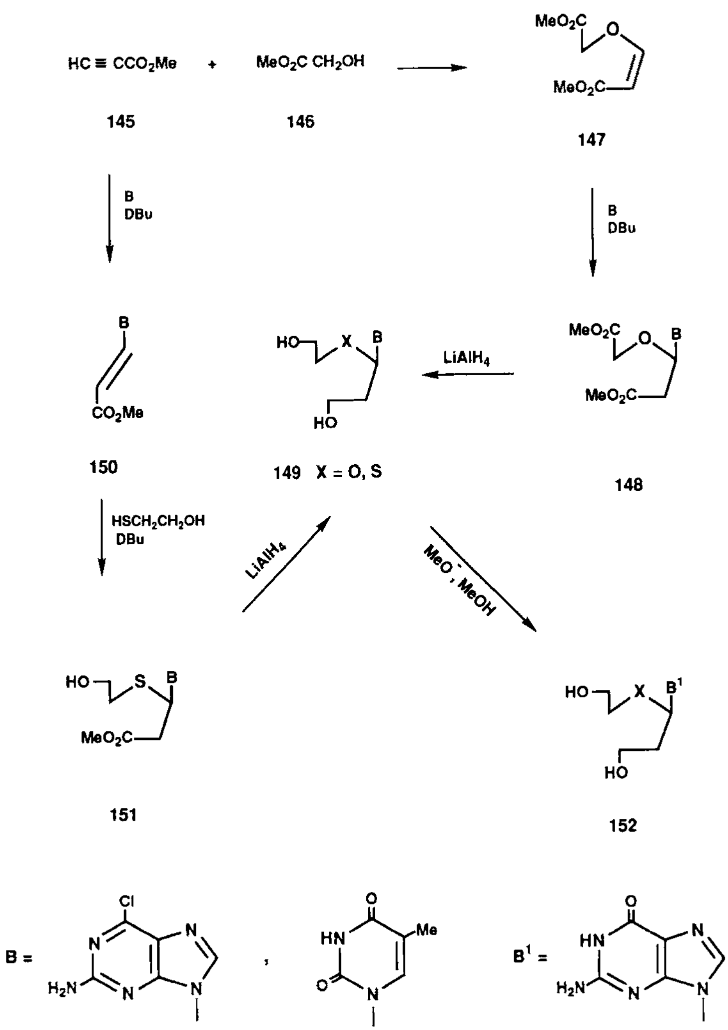
Condensation of **132** with silylated bases gave the corresponding nucleosides **138** in an α/β ratio of 75/25. Anomerization of the α isomer can be performed by stirring in the presence of TMSOTF. Debenzoylation of **138** followed by periodate oxidation and reduction gave **139** (91MI9). The enantiomers of 3′,4′-*seco*-2′-deoxythymidine were similarly prepared (88KGS947). The 2-fluoro analogues were similarly prepared from **133** for a series of nucleosides (91MI9, 91MI14).

R = OH; B = Th, Cy, Ad-9, Ad-3, 3-(ethoxycarbonyl) -1, 2, 4-triazole
R = H; B = Th, Cy, Ad-9, Ad-3, Gu.

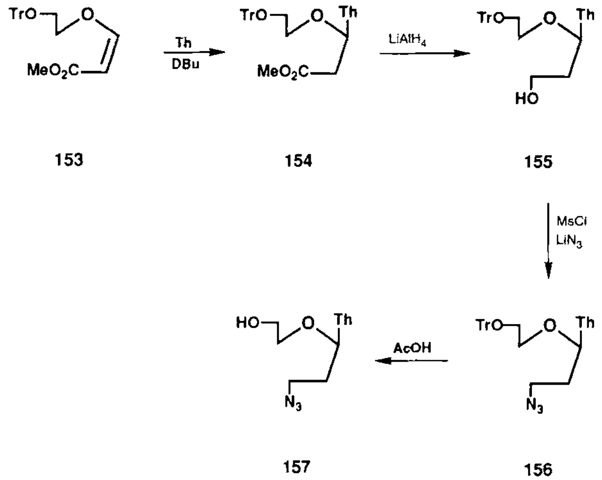
SCHEME 24

The alkylation of bases with 1,4,5,6-tetraacetoxy-3-oxahexane **141** in presence of stannic chloride followed by deacetylation gave **143** (87MI3; 88MI4). The respective 2′-deoxy analogues **144** were similarly prepared from **142** (88MI5). A number of dideoxy and deoxy chloro analogues of ribavirin were similarly prepared (87MI3).

Methyl-*E*-3-(methoxycarbonyl)methoxypropenoate (**147**), obtained by the addition of methyl glycolate (**146**) to methylpropiolate (**145**), underwent a Michael-type addition with 2-amino-6-chloropurine to give **148.** Reduction



SCHEME 25



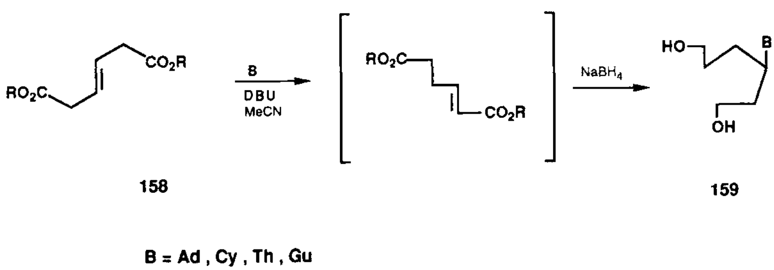
SCHEME 26

of **148** gave **149,** whose subsequent treatment with base gave **152** (89MI10). The sulfur analogues were prepared by conjugate addition of the base to methyl propiolate to give **150,** which served as a Michael acceptor for 2-mercaptoethanol, giving **151.** Reduction of **151** followed by treatment with base gave **152** (X = S). These nucleosides were inactive against herpes simplex types 1 and 2, human cytomegalovirus, and Varicella-Zoster, and ureactive as substrates for HSV-1 thymidine kinase phosphorylation.

Michael-type addition of thymine to **153** gave **154,** whose reduction gave **155.** Conversion of **155** to **156** and detritylation gave **157** as an analogue of AZT (89JMC73).

3. *Carboacyclic Analogues*

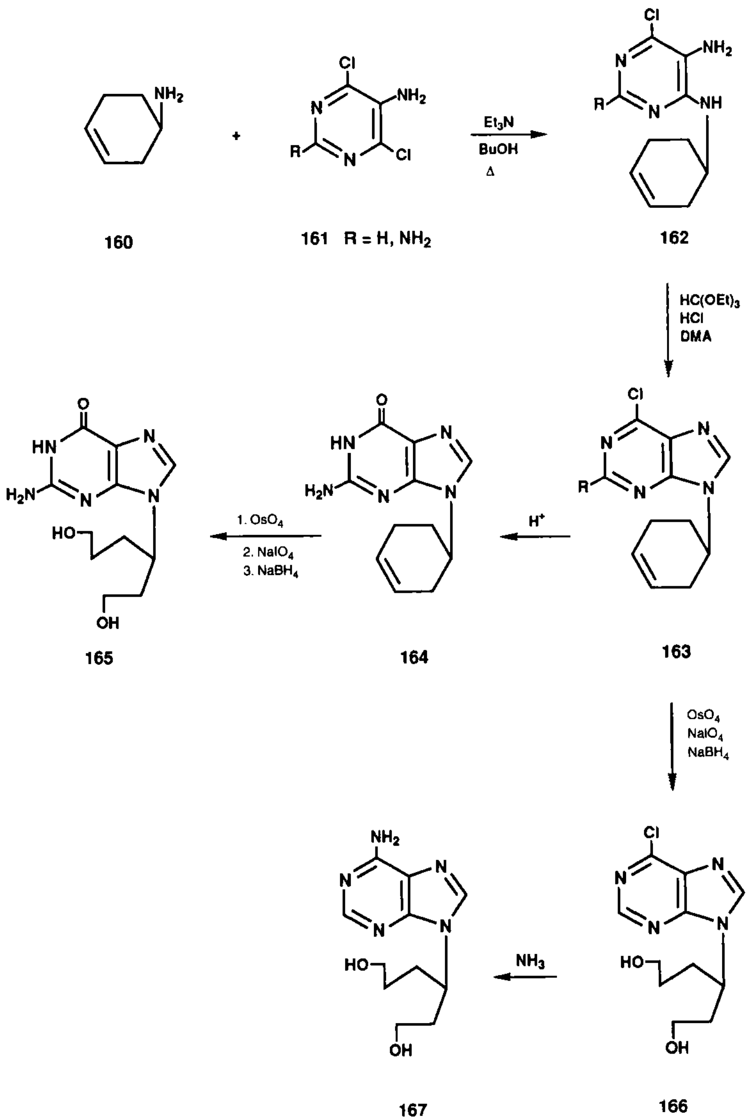
The carboacyclic nucleoside **159** was prepared from (*E*)-3-hexene-1,6-dioate (**158**) by a nucleophilic conjugate addition of nucleobases followed



SCHEME 27

by reduction to give **159** (92MI2). Reduction was carried out with sodium borohydride or $LiAlH_4$, depending on the base. Acetylation and deacetylation may be used to purify the product.

The synthesis may be started by constructing the heterocyclic ring. Thus, reaction of the amine **160** with **161** gave **162**, whose cyclization gave **163**.

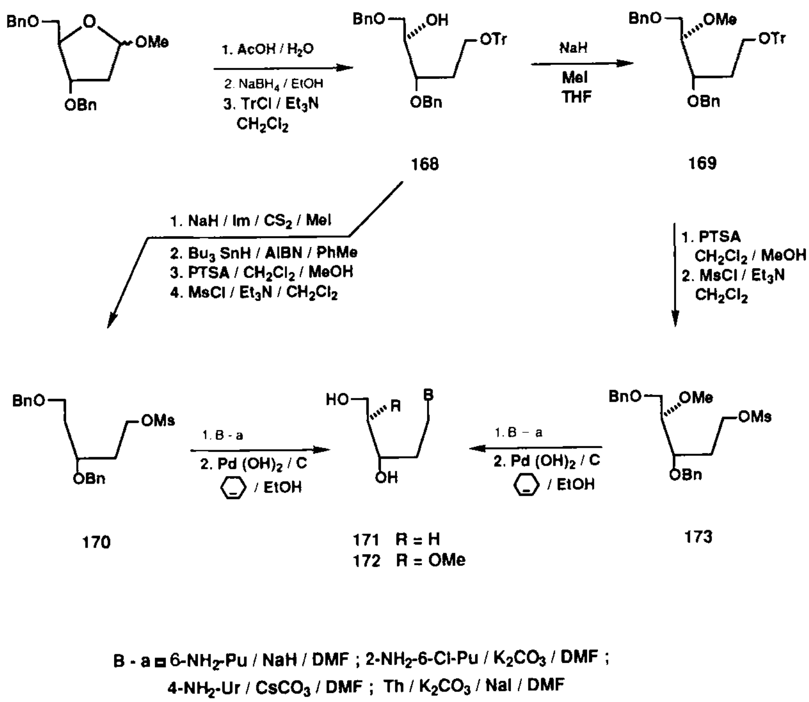


SCHEME 28

Hydrolysis of **163** (R = NH_2) gave **164,** which upon hydroxylation, periodate oxidation, and reduction gave **165** (90JHC1801). However, the hydroxylation of **163** (R = H), periodate oxidation, and reduction gave **166,** which upon reaction with ammonia gave **167.** None of **165** and **167** exhibited antiviral activity *in vitro* against HSV-1, HCMV, and HIV-1.

D. 1′,x-*Seco*-Nucleosides (Type 1.4)

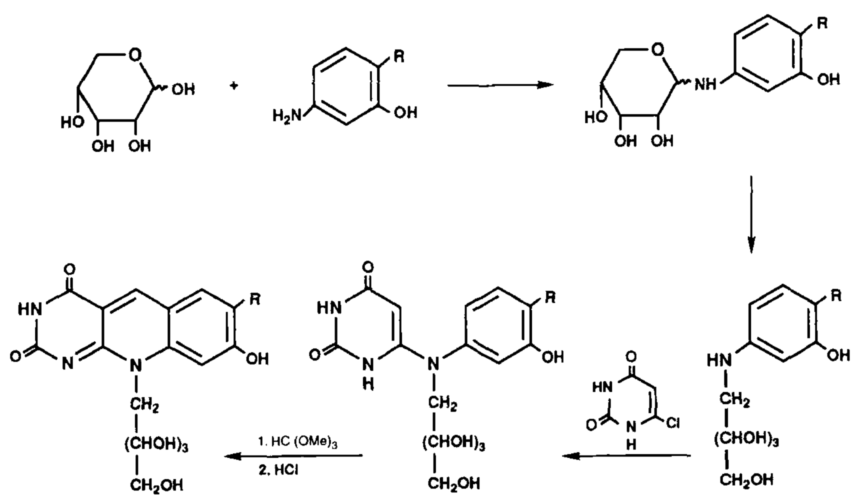
The precursor for this type of nucleoside was 3,5-di-*O*-benzyl-1-*O*-trityl-2-deoxy-D-ribitol (**168**), which was obtained from 1-*O*-methyl-2-deoxy-D-ribofuranose by benzylation followed by deprotection of the *O*-glycoside function, reduction with $NaBH_4$, and protection with a trityl group to give **168.** The secondary hydroxyl group was removed by converting it to the *S*-methylxanthate, followed by a Barton-type reduction. Detritylation followed by mesylation gave **170.** However, methylation of **168** gave **169,** whose detritylation and mesylation gave **173.** Both **170** and **173** were used



Scheme 29

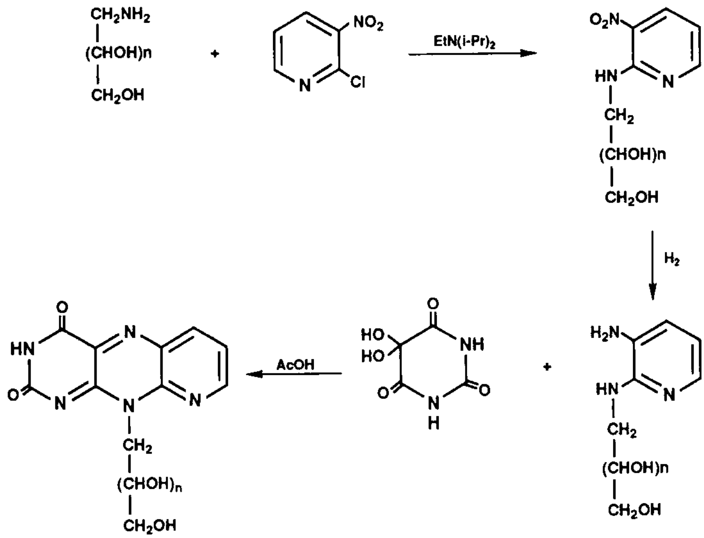
as alkylating agents for the different purine and pyrimidine bases. The adenosine analogues were obtained by reaction with the sodium salt of adenine. Reaction with 2-amino-6-chloropurine in the presence of K_2CO_3 afforded the 9-isomers together with their N-7 isomers. The conversion to the guanosine analogue was also achieved via the *O*-benzyl derivative. This compound was then hydrogenated to give the fully debenzylated guanine derivative. The cytosine analogues were obtained by a reaction with cytosine in DMF in the presence of $CsCO_3$. The *O*-alkylated analogues were formed as side-products. For the synthesis of the thymidine analogues, thymidine was silylated with hexamethyldisilzane (HMDS) in presence of a catalytic amount of $(NH_4)_2SO_4$. The major product isolated was characterized as the N-1 alkylated thymine. The mesylate **173** was reacted with thymine in presence of K_2CO_3/NaI in DMF to give the N-1 alkylated thymine as the major product. The benzyl protecting groups were finally removed by transfer hydrogenation to give the fully deprotected acyclic nucleoside analogues **171** and **172** (92JMC1458). Note that the analogues **171** belong to the 2.6 type, where two bond disconnections are apparent.

7,8-Didemethyl-8-hydroxy-5-deaza*ribo*flavin (**174**), the flavin moiety of *Methanobacterium* coenzyme F_{420} and its 7-methyl analogue could be considered under this type of nucleoside. They were prepared by an acid-catalyzed reaction of an appropriately substituted 6-(*N*-D-ribitylanilino)uracils with trimethyl or triethyl orthoformate followed by deprotection as



174

SCHEME 30

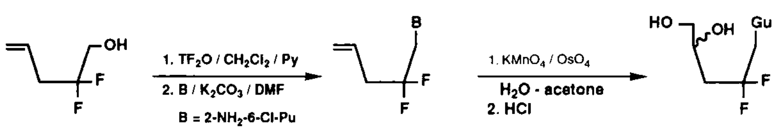


175

SCHEME 31

shown in Scheme 30 (80JHC1709). The pyrido[3,2-*g*]pteridine analogues **175** were prepared by the alkylation of alditolylamines by suitable 2-chloro-3-nitropyridine, followed by reduction and cyclization with alloxan as shown in Scheme 31 (73JHC209).

The fluorinated acyclonucleosides **177** were prepared from 2,2-difluoro-4-penten-1-ol by transforming it to the triflate and then reacting the latter with the base to give **176,** whose hydroxylation gave **177** (91TL3823). These nucleosides were tested and found to be less active than acyclovir.



176 177

SCHEME 32

E. 4′,x-*Seco*-Nucleosides (Type 1.5)

1. *Acyclo-N-nucleoside Analogues*

Examples of this type of nucleoside are rare. However, a variety of analogues whose 4′-position carries a hydroxy group have been reported. Acetylated aldose dialkyl dithioacetals underwent replacement of one alkylthio group by bromine to give **178,** followed by reaction with a number of silylated or mercury salts of heterocyclic compounds and saponification to give acyclic sugar nucleosides **179** [71MI1; 72MI2, 72MI3, 72MI4; 74JCS(CC)729; 75ANY131; 75AX(B)2250; 79MI2; 80MI3, 80MI4, 80MI5, 80MI6; 82MI1].

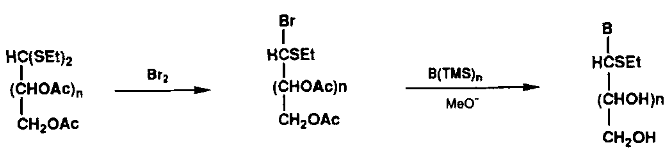
When **180** was subjected to acetolysis it gave an acyclic derivative, which when submitted to nucleosidation gave the acyclic nucleoside **181** (90-JOC3772). However, reaction of methyl-2-3,5-tri-*O*-benzoyl-α-D-arabinoside with silylated pyrimidines in the presence of TMS triflate gave the acyclic nucleoside **183** in addition to **182** (92S1299).

Acyclonucleoside analogues could be obtained as intermediates for the synthesis of AZT by treating a protected nucleic acid base with the acetal (2*S*, 3*S*)-$HOCH_2CH(OH)CHN_3CH_2CH$ $(OBn)_2$ (92MIP1).

The reaction of the pyranosylamine with dimethylformamide dimethylacetal gave **184,** whose reaction with α-amino-α-cyanoacetamide gave **185,** together with the acyclic nucleoside **186,** whose cyclization with ethylformate gave the hypoxanthine **187** [75JCS(CC)47; 77JCS(P1)1094].

2. *Acyclo-C-nucleoside Analogues*

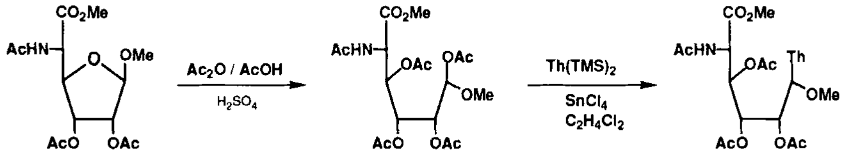
Fusion of 2-trimethylsilylpyridine and aldehydes **188** or **190** gave after deprotection the respective acyclic nucleosides **189** (88MI7). Similarly, 2,4:3,5-di-*O*-benzylidene-D-ribose reacted with 2-trimethylsilylpyridine and 1-methy-2-trimethylsilylimidazole (72ABC1443).



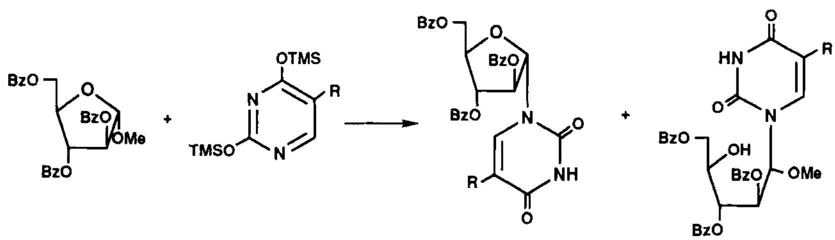
178 179

B = 5-F-Ur , Th, Cy, Ad, 6-Cl Pu, 6-thio-Pu

Scheme 33

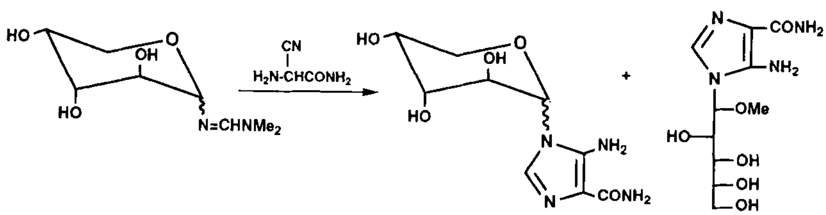


180 181

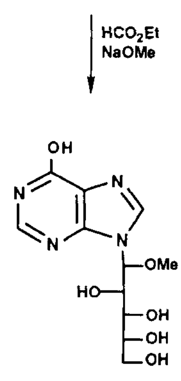


182 183

Scheme 34

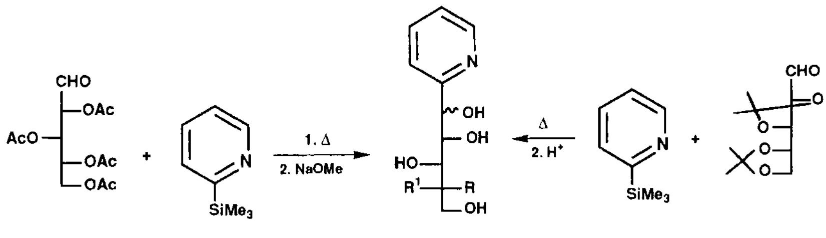


184 185 186



187

Scheme 35



188 189 190

SCHEME 36

Reaction of the ketoacid **191** with amidines gave the respective pyrimidine acyclo-*C*-nucleoside analogues, which could be deprotected by acid to give **192** (84AQ45).

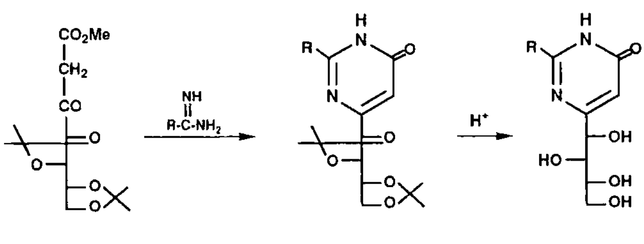
The glutarimide ring was constructed by reacting the aldehyde **193** with (carbomethoxy methylene) triphenylphosphorane to give **194**, which underwent Michael addition with malonamide ester to give **195.** Hydrolytic decarboxylation gave **196**, whose debenzylation gave **197** (92CJC1662).

Several *C*-nucleosides have been prepared by Pictet–Spengler condensations between biogenic amines, such as dopamine hydrochloride **198** with D-glucose **199** to give **200** (83CJC2721).

The pyrrole **203** was prepared by reducing the phenylosazone **201** to give 1-amino-1-deoxy-D-*gluco*heptulose (**202**) followed by reaction with ethyl acetoacetate (76AQ855).

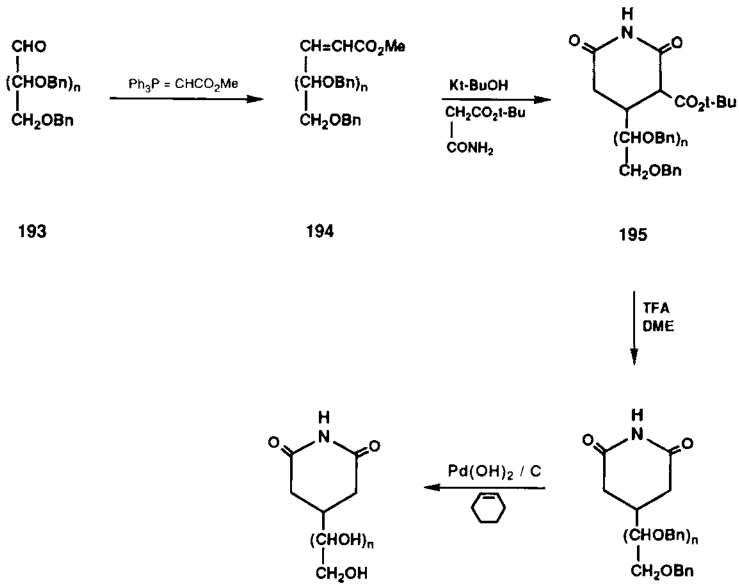
The reaction between 2-amino-2-deoxyaldose (**204**) and cyclic β-dicarbonyl compounds such as **205** or acyclic ones yielded polyhydroxyalkylpyrroles **206** and **207**, respectively [74AQ1082; 80MI1; 87AQ(C)271].

Reaction of the diacetonide of D-*mannono*lactone **208** with lithium acetylide gave the lactol of actylenic ketone, which with hydrazine was transformed into the pyrazole **209.** This, upon acetolysis, gave **210**



191 192

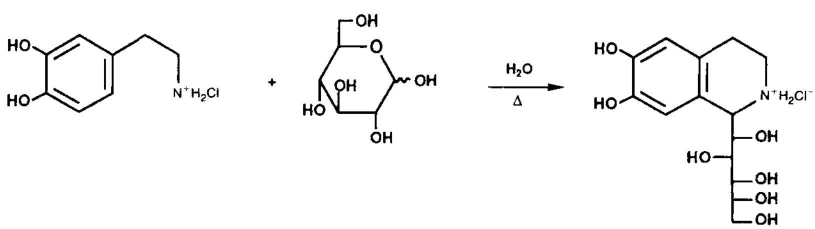
SCHEME 37



193 194 195

197 196

SCHEME 38

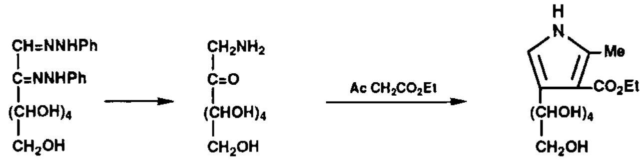


198 199 200

SCHEME 39

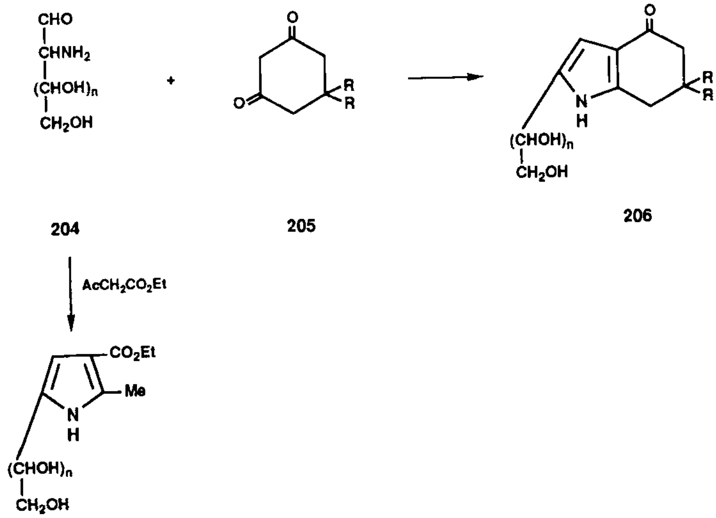
[77JCS(P1)1786; 79JCS(P1)244; 81JCS(P1)2258; 85MI1]. Deoxychloro derivatives of the polyol residues were prepared [92JCR(S)38].

Chain elongation of gluconic acid, using the *C*-phenylglycine method, led to an attachment of an allyl residue as in **211,** whose acetylation gave **212.** Oxidative cleavage of the allylic double bond led to 1,3-dicarbonyl compound **213,** which can be converted with a 1,2-dinucleophile such as phenylhydrazine to **214** and **215.** The reaction with glycaric acid **216** gave



201 202 203

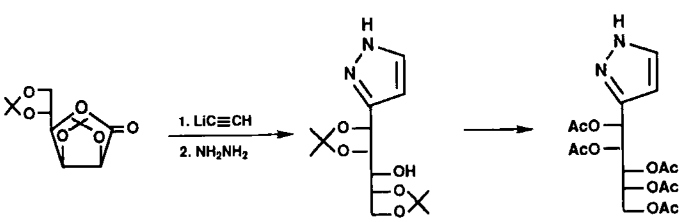
SCHEME 40



204 205 206

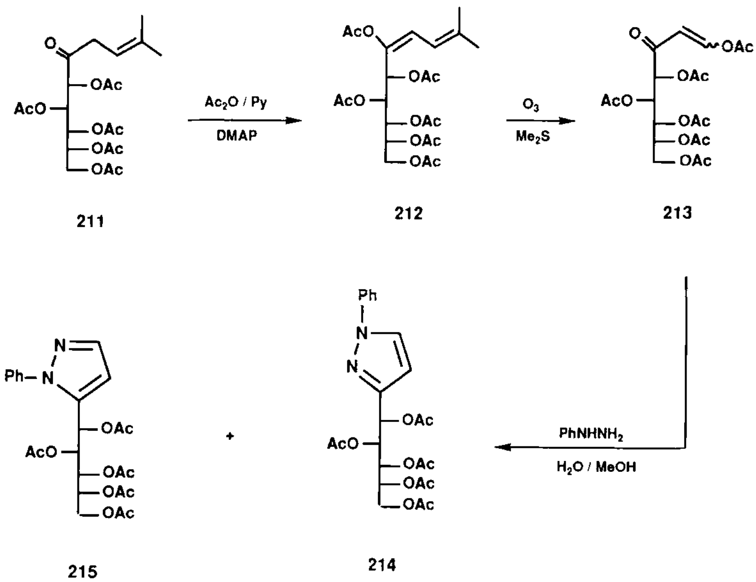
207

SCHEME 41



208 209 210

SCHEME 42



SCHEME 43

217. Rearrangement of **217** formed **218,** which oxidized to **219,** which cyclized with hydrazine to give **220** (89LA247).

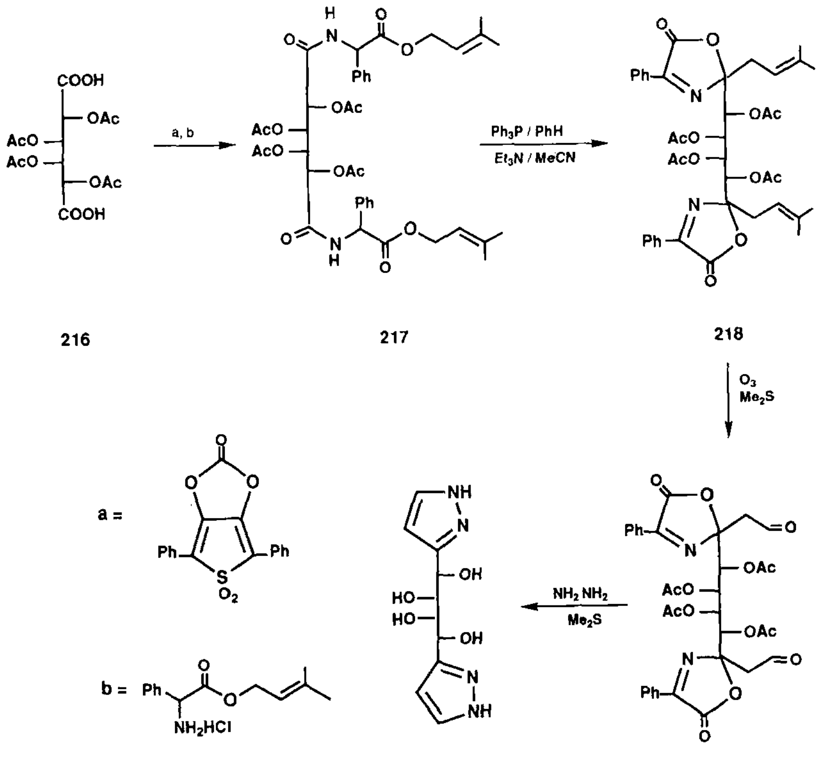
The reaction of saccharide hydrazones with nitro-olefins gave the pyrazole **221** (88MI3; 89MI6). The reaction of 1-nitro-1,2-dideoxyhept-1-enitol **223** with formaldehyde phenylhydrazone and *p*-tolylhydrazones gave the pyrazoles **222** and **224,** respectively (89MI6; 90AX1718; 91MI1, 91MI6).

The cycloaddition of **223** with diazoethane in 1,4-dioxane gave the nitropyrazoline **227,** whose aromatization was effected with HCl to give pyrazole **228** (91MI7). 3-Methyl-2-(4-nitrophenyl)-4-phenyl-1,3-oxazolium-5-olate (**226**) reacted regioselectively with **223** to give the respective pyrrole derivatives **225,** which could be deacetylated with sodium methoxide (89MI4).

1,3-Dipolar cycloaddition of the diazoketones **229** or **230** with methyl propiolate or dimethyl acetylenedicarboxylate gave the respective pyrazole **231** (67CCC3787).

1,3-Dipolar cycloaddition of several diazoketones **232** to benzyne gave the indazoles **233** (76JHC1241).

Reaction of imidazolidine-2-thione **234** with benzyl chloride gave the acyclic *C*-nucleoside **238** (84MI2). Acid-catalyzed isomerization of imidazolines **235** gave imidazoles **237** via **236,** which can be also obtained by reductive desulfurization of **238** (84MI2, 84MI3). However, acid-catalyzed isom-



216 217 218

219 220

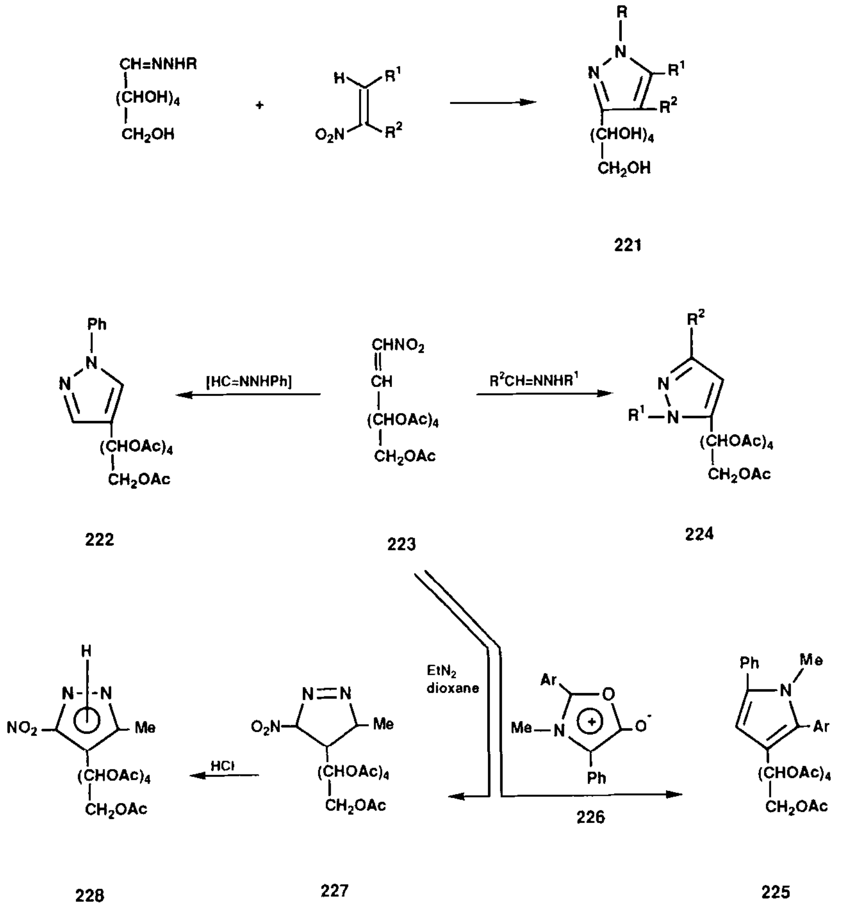
SCHEME 44

erization of **234** gave the open-chain analogue of 4-imidazoline-2-thione (88MI8).

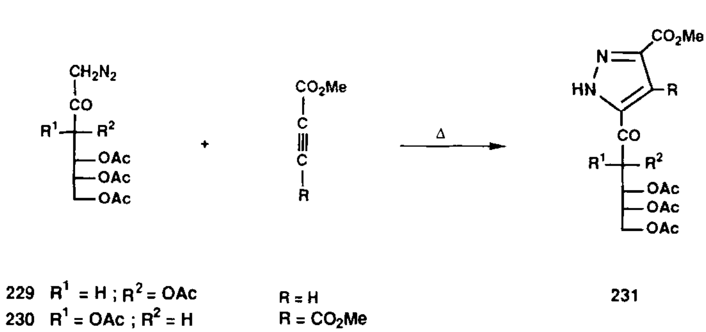
Reaction of the α-haloketoses **239** with thioamides gave **240** (75MI2).

The reaction of the amide **243**, obtained from the reaction of the acid chloride **241** with **242**, with thiosemicarbazide gave the triazole **244** and with phenylhydrazine the triazole **245**. Both of them deprotected to give **246** (R^1 = H or Ph) (86PHA551).

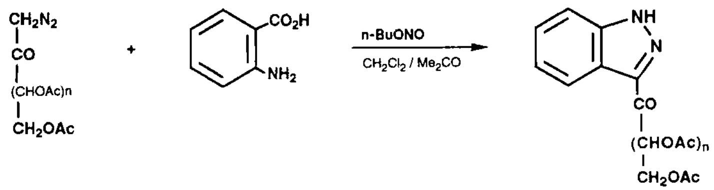
The acyclic *C*-nucleoside analogues of 1,3,4-thiadiazoles **247** were prepared by the oxidative cyclization of the thiosemicarbazones **248** (X = S) with iron(III) chloride (86JPR1; 87BCJ3405). The respective oxadiazole analogues were prepared by the oxidation of the acetate of **248** (X = O) with iodine (72MI1). Both of the aroylhydrazones and thiosemicarbazones



SCHEME 45

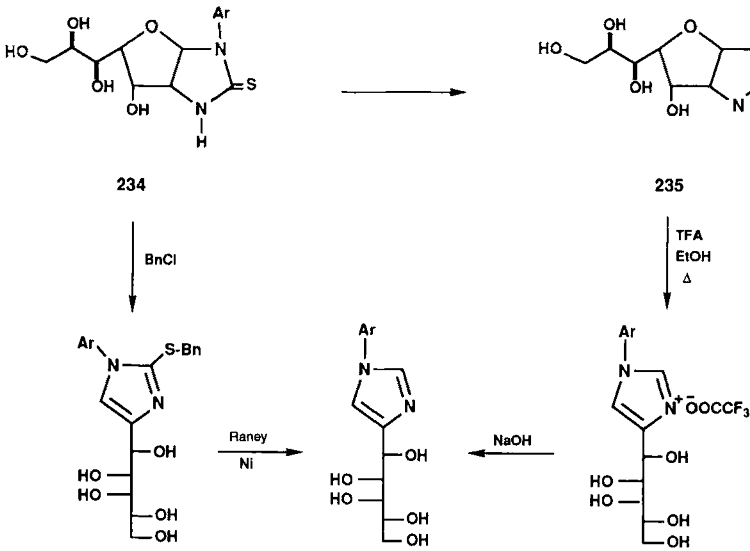


SCHEME 46



232 233

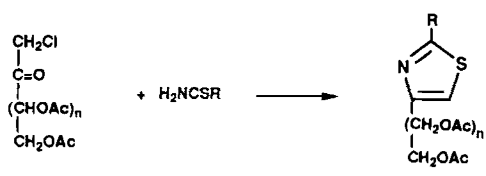
SCHEME 47



234 235

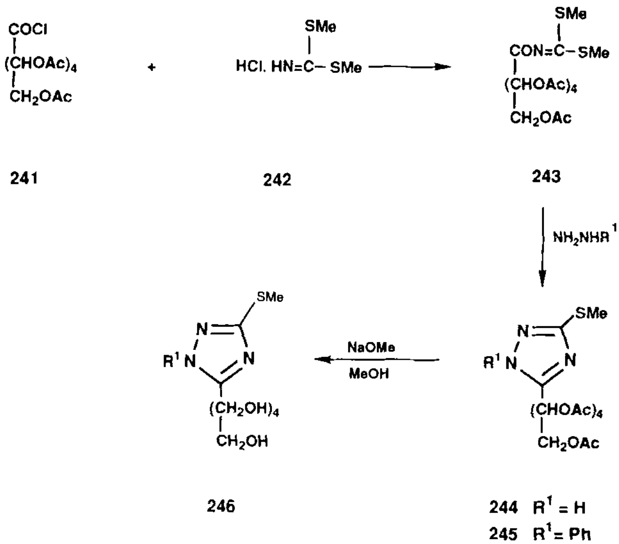
238 237 236

SCHEME 48

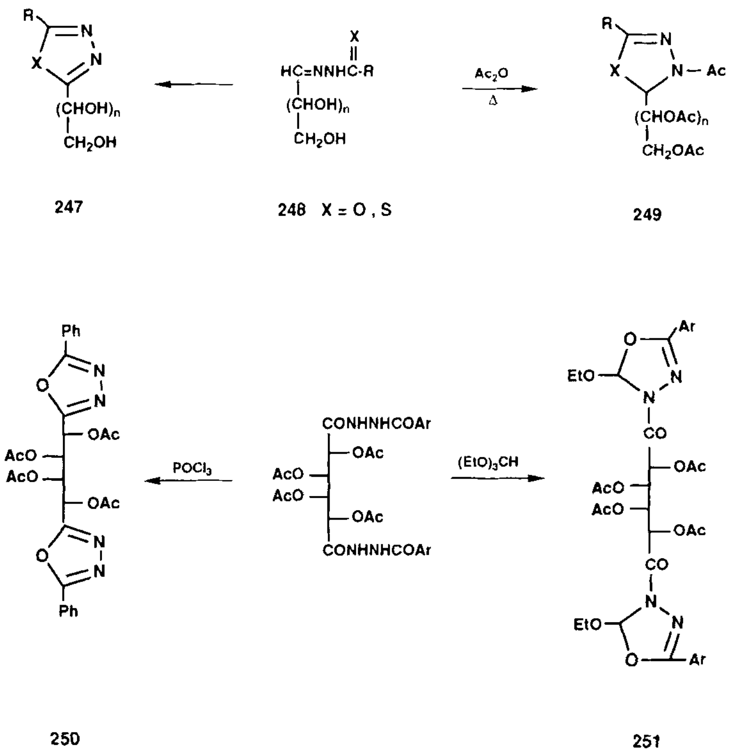


239 240

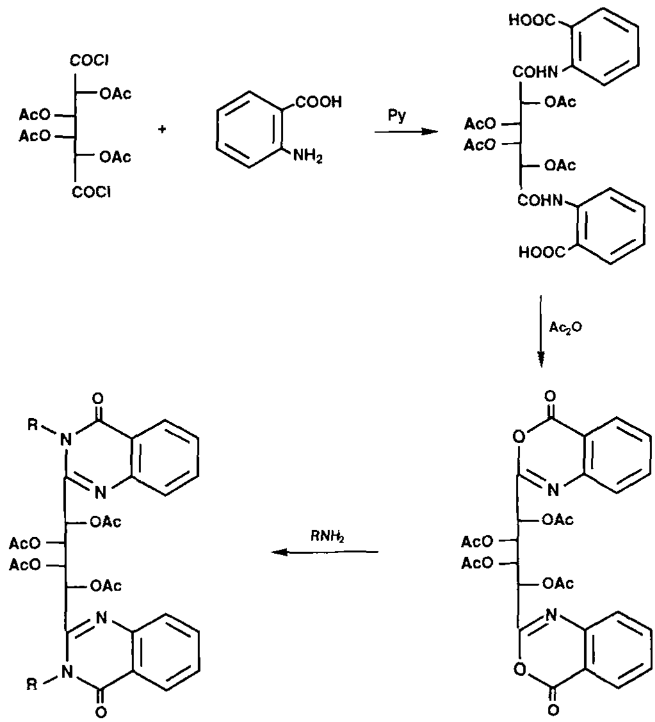
SCHEME 49



SCHEME 50



SCHEME 51



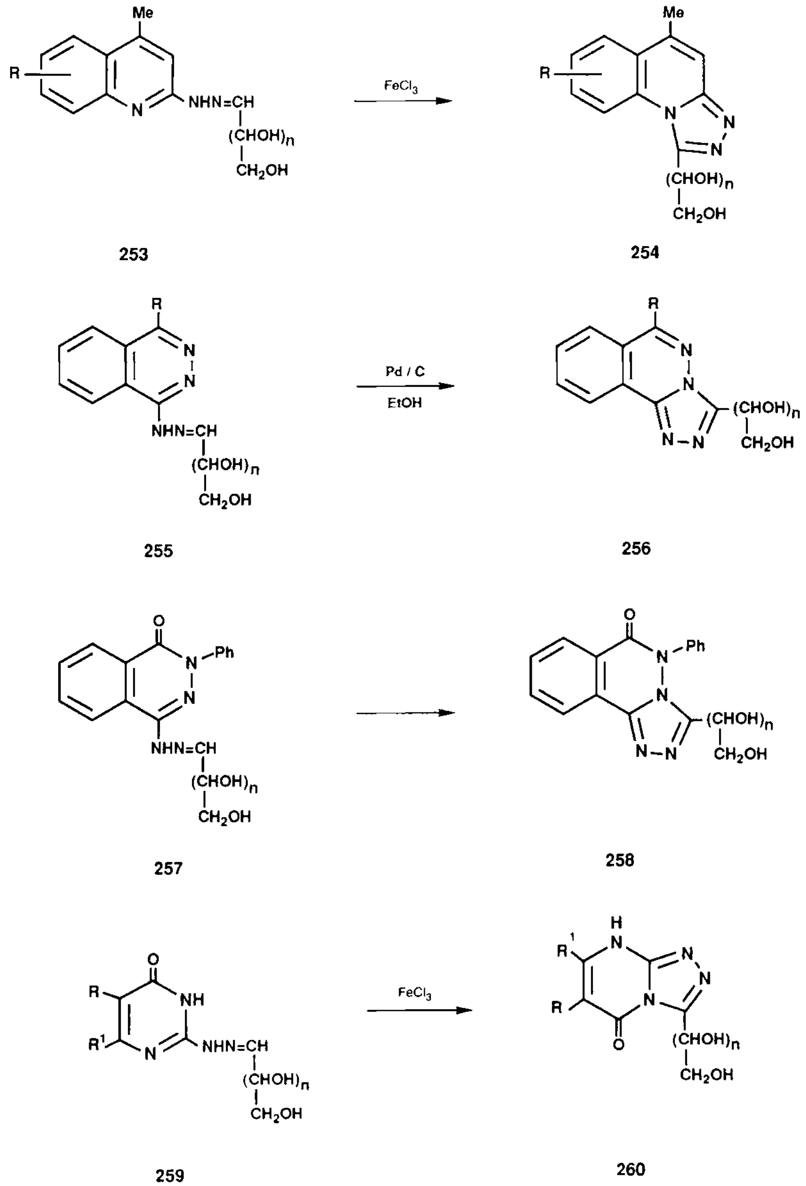
252

SCHEME 52

underwent cyclization with acetic anhydride to the oxadiazolines and thiadiazolines **249**, respectively (77MI1; 78MI1; 79MI1, 79MI3, 79MI4; 80MI2; 83MI4; 87MI2; 88MI2, 88MI6). The oxadiazoles **250** could be prepared from the dehydrative cyclization of the respective hydrazide (75MI1), and the oxadiazolines **251** from cyclization with triethyl orthoformate (77-OPP267).

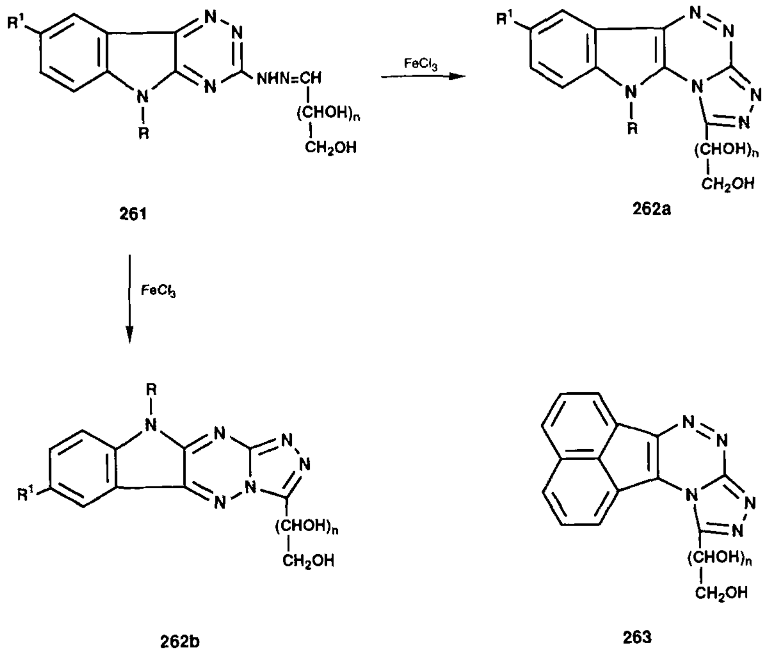
Condensation of tetra-*O*-acetylgalactaroyl chloride with anthranilic acid gave the respective diamide, which upon dehydrative cyclization with Ac_2O gave the corresponding dibenzoxazine derivative. Reaction of the benzoxazine with amines gave a novel type of double-headed acyclic quinazolines **252** (82MI3; 87MI4).

Catalytic dehydrogenative cyclization of the sugar heterocyclic hydrazones with Pd/C or $FeCl_3$ gave the respective 1,2,4-triazolo heterocyclic analogues. Thus, the appropriate quinoline **253** gave **254** (94MI1), phthalazine **255** formed **256** (91MI8), and phthalazinone **257** gave **258** (96UP1).



SCHEME 53

The pyrimidine **259** gave **260** (96UP2). The triazine **261** gave **262a** or **262b**, depending on the substituent or the method of formation (92BCJ546; 93SPL1817; 94AHC207, 94SPL677; 96UP3, 96UP4). Similarly, the con-



SCHEME 54

densed triazolotriazine **263** was prepared from the oxidative cyclization of the respective hydrazone (94BCJ149). Earlier work on the synthesis of acyclic derivatives of heterocyclic compounds was reviewed (70MI1).

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